Stereoselective Synthesis of Functionalized Quaternary Stereocenters, Naturally Occurring Tetronic Acids and (–)-(*R*,*R*)-L-Factor

by

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To My Family

Abstract

The enantioselective synthesis of functionalized, acyclic, quaternary stereocenter-containing building blocks was achieved from diastereomerically pure alkylidenemorpholinones by employing Suzuki-Miyaura cross-coupling and Prins reactions as the key steps. In a separate approach, the enantioselective conjugate addition of a variety of 3-alkyl-and/or 3-aryl tetronic acids or 3-alkyl-and/or 3-aryl tetramic acids to *α*,*β*-unsaturated systems catalyzed by chiral aminothioureas, aminosquaramides and cinchona alkaloids was examined. These studies provided the quaternary stereocenter-containing furan-2,4-diones and pyrrolidine-2,4-diones with moderate enantiomeric excess.

A variety of 3-aryl tetronic acids were synthesized by employing an undirected, intermolecular C−H functionalization reaction of arenes with 3-diazofuran-2,4-dione as the key step. This method was applied in the synthesis of a series of biologically active, naturally occurring 3-aryl-5-arylidene tetronic acid derivatives such as pulvinic acids and pulvinones.

A concise synthesis of (−)-(*R*,*R*)-L-factor was achieved in four steps by using an organocatalytic asymmetric direct vinylogous aldol reaction of *γ*-crotonolactone and hexanal as the key step.

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my advisor Prof. Sunil V. Pansare for his continuous support of my Ph. D. studies and research, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me throughout my programme and during the writing of this thesis. I have been extremely lucky to have a supervisor who cared so much about my work, and who responded to my questions and queries so promptly. I could not have imagined having a better supervisor for my Ph. D. studies.

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List of Abbreviations and Symbols

Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
APPI	atmospheric pressure photoionization
aq.	aqueous
BAIB	bis(acetoxy)iodobenzene
BINOL	1,1′-dinaphthalene-2,2′-diol
bmim	1-butyl-3-methylimidazolium
BnBr	benzyl bromide
Boc	*tert*-butoxycarbonyl
br	broad
BzCl	benzoyl chloride
CAN	ceric ammonium nitrate
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DABN	(*S*)-(–)-2,2′-diamino-1,1′-binaphthalene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide

DCE	1,2-dichloroethylene
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
EI	electrospray ionization
eq.	equivalent (s)
ESI	electrospray ionization
esp	$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenediproponoate
EtOAc	ethyl acetate
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
g	gram (s)
h	hour (s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HWE	Horner-Wadsworth-Emmons

Hz	Hertz (s)
i-Bu	isobutyl
IBX	2-iodoxybenzoic acid
Ipc	diisopinocampheyl
IR	infrared
J	coupling constant
L	ligand
LAH	lithium aluminium hydride
LCPA	lithium *N*-cyclohexyl-*N*-isopropylamide
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
LICA	lithium isopropyl cyclohexylamide
LiDBB	lithium di-*tert*-butylbiphenylide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
M^+	molecular ion
Me	methyl
mg	milligram(s)
MIDA	*N*-methylimidodiacetic
min	minute (s)
mL	milliliter (s)
mmol	millimole (s)
mp	melting point

MS	mass spectrum
MsCl	methanesulfonyl chloride
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PTSA/*p*-TsOH	*para*-toluenesulphonic acid
R_f	retention factor
rt	room temperature
TBAF	tetra-n-butylammonium fluoride
TBDMS/TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UV	ultraviolet

α	alpha
β	beta
γ	gamma
δ	chemical shift (in NMR spectroscopy)

Chapter 1

Enantioselective Synthesis of Functionalized Quaternary Stereocenters from Chiral Alkylidenemorpholinones

The work described in this chapter has been published in the European Journal of Organic Chemistry:

Manchoju, A.; Thorat, G. R.; Pansare, S. V. *Eur. J. Org. Chem.* **2015**, 5939.

Most of the synthetic work described in this chapter was carried out by A. Manchoju

Preliminary studies on the synthesis of one of the bromoalkylidene morpholinones described in this chapter and its cross-coupling reactions were conducted by R. G. Thorat.

1.1 Introduction

Quaternary stereocenters are interesting structural motifs which present a unique synthetic challenge. They are encountered as structural units in several natural products and hence enantioselective approaches to quaternary stereocenters have been intensely investigated in recent years.[1] Several non-catalytic[2] as well as catalytic[3] enantioselective methods have been developed for assembling quaternary stereocenters. While some of these efforts are in the realm of natural product synthesis,[1a,c] other studies showcase methodology for the construction of quaternary stereocenters by employing suitably functionalized starting materials.[1d,2,3]

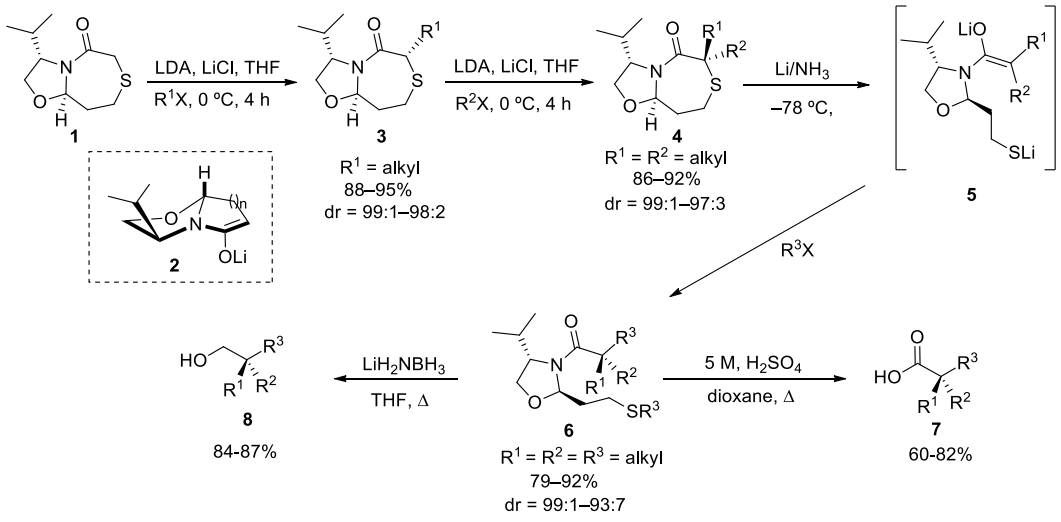
In this context, opportunities exist for the construction of quaternary centers in acyclic fragments that have functionality for further elaboration.[4] To explore this prospect, we chose to examine the synthesis of hydroxy aldehydes and carboxylic acids with a quaternary α-stereocenter. The following section provides a summary of the auxiliary-based syntheses of functionalized quaternary stereocenters reported[2] during the past decade. While several of the recent methods rely on an auxiliary-controlled stereoselective C-C bond forming reaction as the key step, catalytic procedures are also known.[3]

1.2 Recent reports on the enantioselective, auxiliary mediated synthesis of quaternary stereocenters

1.2.1 The Gleason synthesis of acyclic quaternary stereocenters

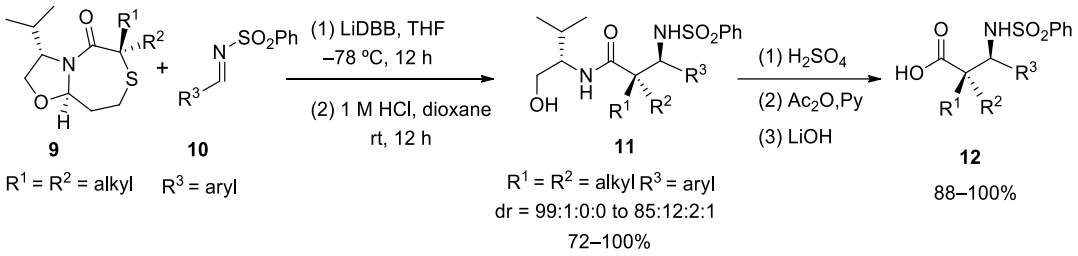
In 2006, Gleason and coworkers[2e] developed a methodology for the synthesis of acyclic quaternary stereocenters from the chiral bicyclic thioglycolate lactam **1**, derived from (*S*)-valinol (Scheme 1.01). The strategy relies on sequential stereoselective alkylations of an amide enolates derived from **1**. The first two alkylations of **1** with alkyl

halides in the presence of lithium diisopropylamide (LDA) and LiCl furnished **3** in good yields with excellent diastereoselectivities. The high stereoselectivity of alkylations of **1** is due to approach of the electrophile (alkyl halide) from the sterically less hindered *exo* face (convex face) of the lactam enolate **2** (Scheme 1.01). Notably, the authors state that the isopropyl group in **2** occupies a pseudo-equatorial position and hence it has no significant role in facial discrimination of the enolate. Reduction of the dialkylated bicyclic lactams **4** under Birch reduction conditions generates the α,α-disubstituted enolates **5** which were alkylated with alkyl halides to provide **6** in good yields and with high diastereoselectivities. Subsequently, the chiral auxiliary was removed using one of two methods. The first method involves acid hydrolysis of amides in **6** to give the carboxylic acids **7**. In the second method, **6** were subjected to reduction using lithium amidoborohydride to furnish the alcohols **8** (Scheme 1.01).



Scheme 1.01

In 2009, the same group[2f] synthesized the quaternary stereocenter containing β-amino acids **12** from **9** using benzenesulfonyl imines **10** instead of alkyl halides as the electrophiles (Scheme 1.02). The α,α-disubstituted lithium enolates derived from the lactams **9** were treated with imines **10** followed by partial acid-hydrolysis (acetal cleavage) to afford **11**. The valinol portions of **11** (the auxiliary) were removed by a three step hydrolysis which involves, in sequence, N to O acyl transfer under acidic conditions, *N*-acetylation of the resulting amino esters and finally basic hydrolysis of the esters to provide the β-amino acids **12**.



Scheme 1.02

The authors propose that the high stereoselectivity of the Mannich reactions can be explained by a Zimmerman-Traxler transition states (Figure 1.1) assembly. Transition state **14** is destabilized by a *syn*-pentane interaction between one of the enolate substituents and R. The transition state **13** is free from this interaction and is therefore favoured, giving rise to the high diastereoselectivity.

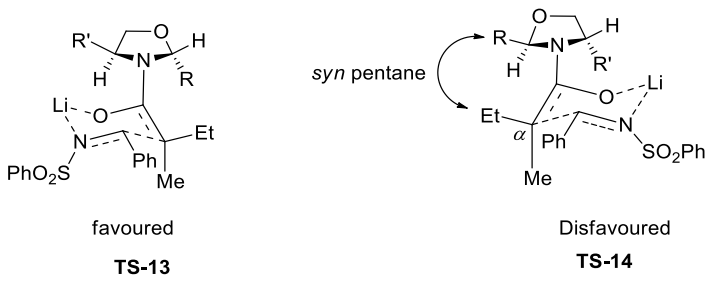
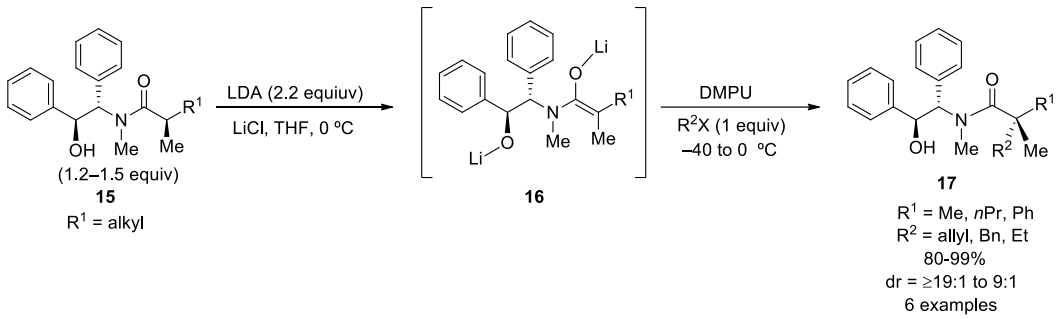


Figure 1.1

1.2.2 The Myers synthesis of functionalized quaternary stereocenters

In 2012, Myers and coworkers[2g] developed the alkylation of chiral amides **15** derived from pseudoephenamine to afford functionalized quaternary stereocenter containing amides **17** with high diastereoselectivities (Scheme 1.03). Amides **15** were synthesized from (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol in five steps. Stereoselective enolization of amides **15** in the presence of LDA gave enolates **16** which were alkylated with various alkyl halides to afford the quaternary stereocenter-containing products **17** in good yields and with high diastereoselectivity (Scheme 1.03).



Scheme 1.03

The high diastereoselectivity of the alkylation reactions can be explained by the transition state (TS) assemblies TS-**18** and TS-**19** shown in Figure 1.2. As shown in TS-**19**,

the top faces of the amides are sterically hindered by a solvated lithium alkoxide side chain and hence the base approaches from the bottom face of the amides (as drawn) to form selectively *Z*-enolates by deprotonation, as shown in TS-**18**. This results in stereoselective enolization of the amides. Similarly, alkylating agents approach the enolates from the less hindered bottom face to provide the alkylation products with high distereoselectivity.

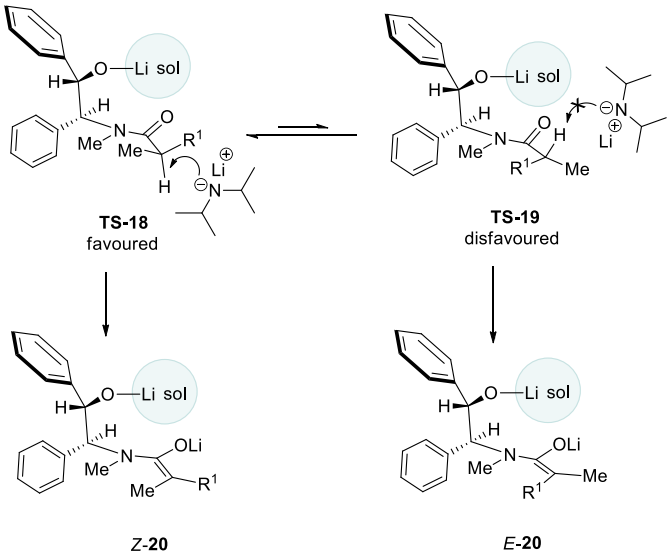
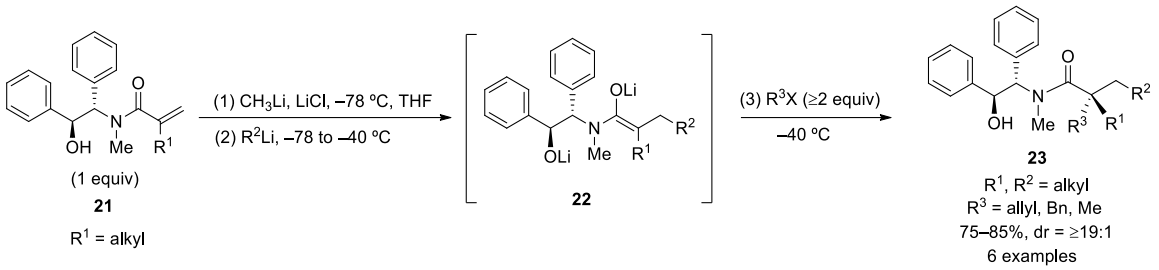


Figure 1.2

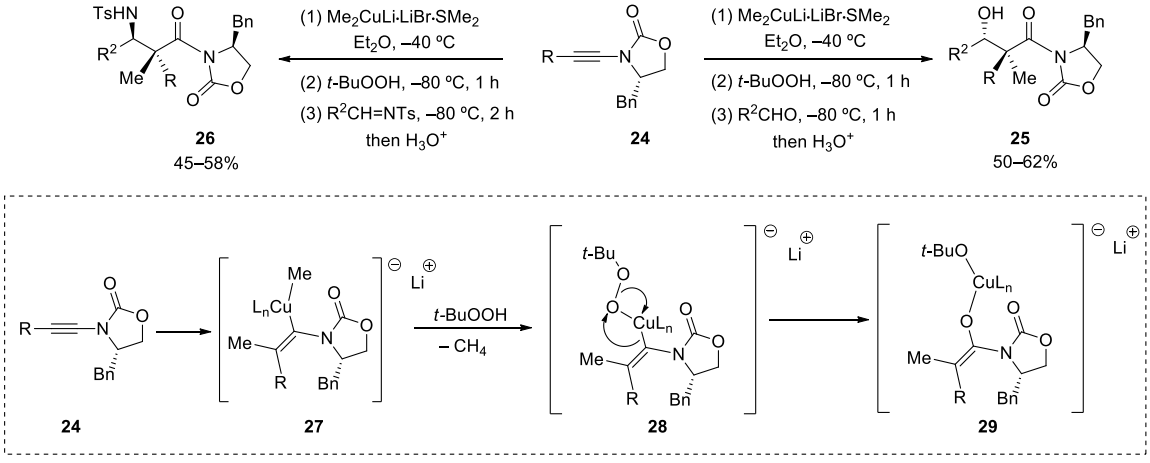
The conjugate addition-alkylation reactions of α-alkyl-α,β-unsaturated pseudoephenamine amides **21** were also examined (Scheme 1.04). The hydroxy groups in amides **21** were first deprotonated with methyllithium (MeLi) followed by a conjugate addition of alkyllithium (R^2Li) to generate the corresponding enolates **22**. Reactions of **22** with alkyl halides under steric control (as shown in Figure 1.2) provided the products **23** in good yield and with high diastereomeric excess.



Scheme 1.04

1.2.3 The Marek synthesis of quaternary stereocenters

In 2013, Marek and coworkers[2d] reported the synthesis of diastereomerically and enantiomerically enriched acyclic systems, with a functionalized quaternary stereocenter, from ynamides **24** *via* aldol and Mannich reactions (Scheme 1.05). This methodology employs the regioselective carbocupration reaction of ynamides **24** with oraganocuparates ($Me_2CuLi{\cdot}LiBr{\cdot}Me_2S$) followed by oxidation using *tert*-butyl hydroperoxide (*t*-BuOOH) to give stereodefined, trisubstituted copper enolates **29**. Reaction of the enolates **28** with aldehydes and sulfonyl imines furnished the aldol products **25** and the Mannich products **26** respectively, both with high diastereoselectivity.



Scheme 1.05

The high stereoselectivity of the reactions of **29** can be explained by Zimmerman-Traxler transition states (chair-like conformation, TS-**30**, TS-**31**, Figure 1.3) in which the benzyl group of the oxazolidinone auxiliary shields one stereoface of the enolate, thereby promoting addition of the electrophile from the other face. Depending on the nature of the electrophile, the oxazolidinone carbonyl group is either coordinated to the copper (as in **31**) or it is not (as in **30**). This conformational change results in a switch of the facial selectivity of the copper enolate.

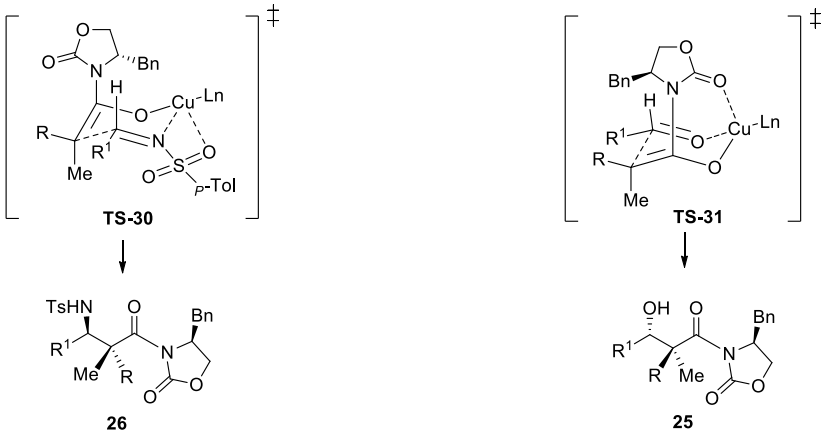
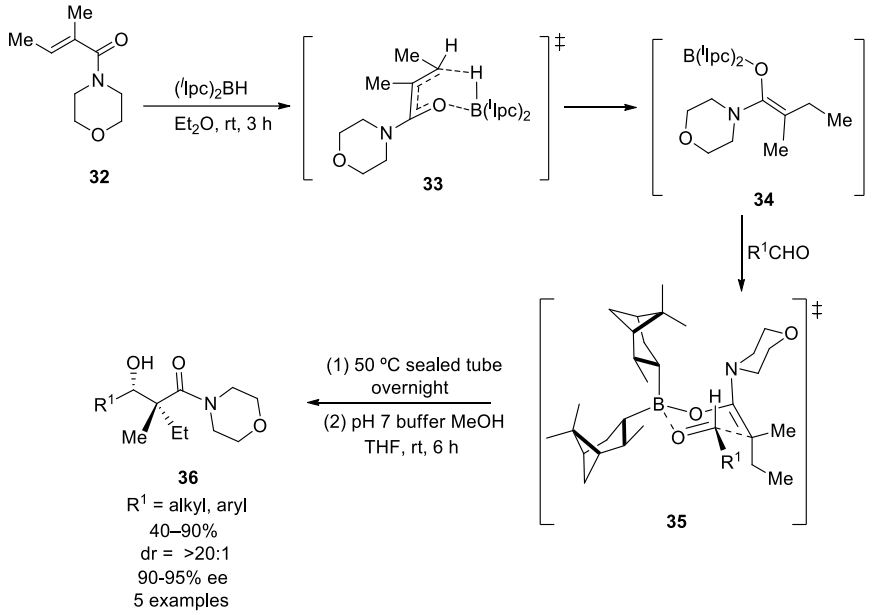


Figure 1.3

1.2.4 The Roush synthesis of functionalized acyclic quaternary stereocenters

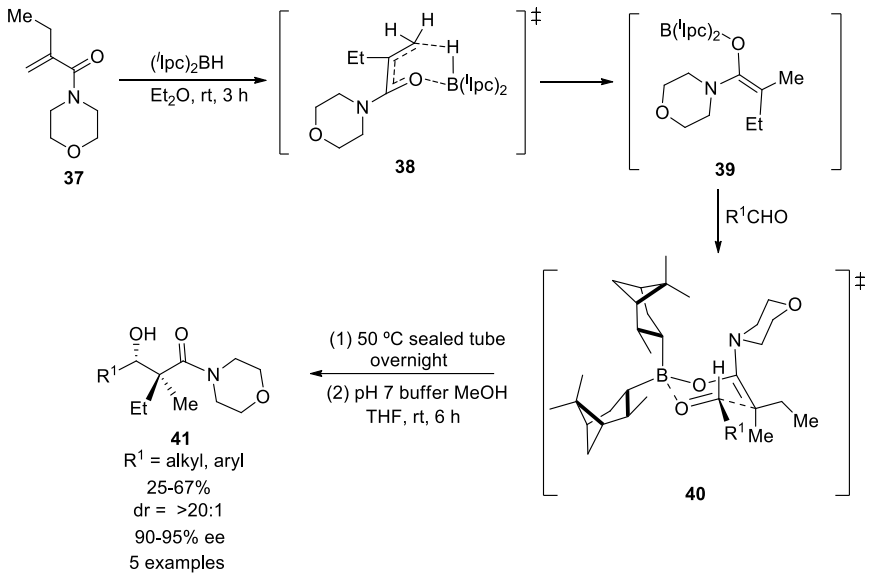
In 2013, Roush and coworkers[2h] developed a methodology for the enantioselective synthesis of functionalized acyclic quaternary stereocenters. The key step in this approach is a stereoselective 1,4 hydroboration of α,β-unsaturated morpholine carboxamides **32** with (diisopinocampheyl)borane ($(^{l}\text{Ipc})_2\text{BH}$, Scheme 1.06) which selectively provides the *Z*-enolborinates **34**. Reaction of **34** with alkyl or aryl aldehydes provides β-hydroxy amides

36 with high diastereo- and enantioselectivity. The authors state that the stereoselectivity of this reaction is due to the formation of a highly organized chair-like transition state assembly **35** (Scheme 1.06).



Scheme 1.06

In related studies, α-ethyl acrylamide **37** was treated with (^{l}Ipc)$_2$BH to give the *E*-enolborinate **39** which furnished the aldol products **41** with high diastereo- and enantioselectivity (Scheme 1.07).



Scheme 1.07

1.3 Objective

The objective of our studies was to develop new methodology for the construction of enantiomerically enriched acyclic motifs that contained functionalized quaternary stereocenters. Such motifs can be used as precursors or intermediates for the synthesis of small organic molecules with quaternary stereocenters or they can be incorporated into more complex structures.

Our approach to the enantioselective synthesis of functionalized quaternary stereocenters is shown in Figure 1.4. The strategy is based on the use of enantiomerically enriched, amino alcohol-derived, bromoalkylidene morpholinones **42** and **43** as the starting materials. The stereoselective cross-coupling reactions of morpholinones **42/43** with aryl or alkyl boronic acids, or their derivatives, should provide the disubstituted alkylidene morpholinones **44**. A stereoselective Prins reaction of the cross-coupling products **44** would generate the spiromorpholinones **45** which contain the target quaternary stereocenter.

Removal of the amino alcohol portion in **45** should provide the enantiomerically enriched, α-hydroxyamides **46** with a quaternary stereocenter (Figure 1.4).

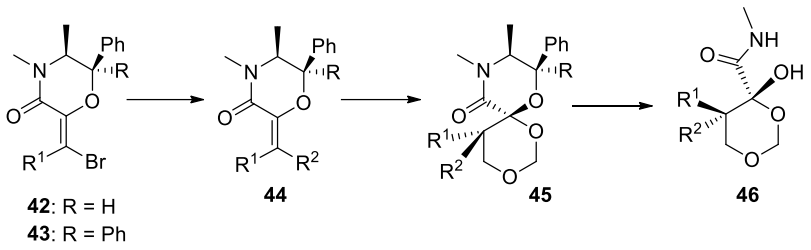
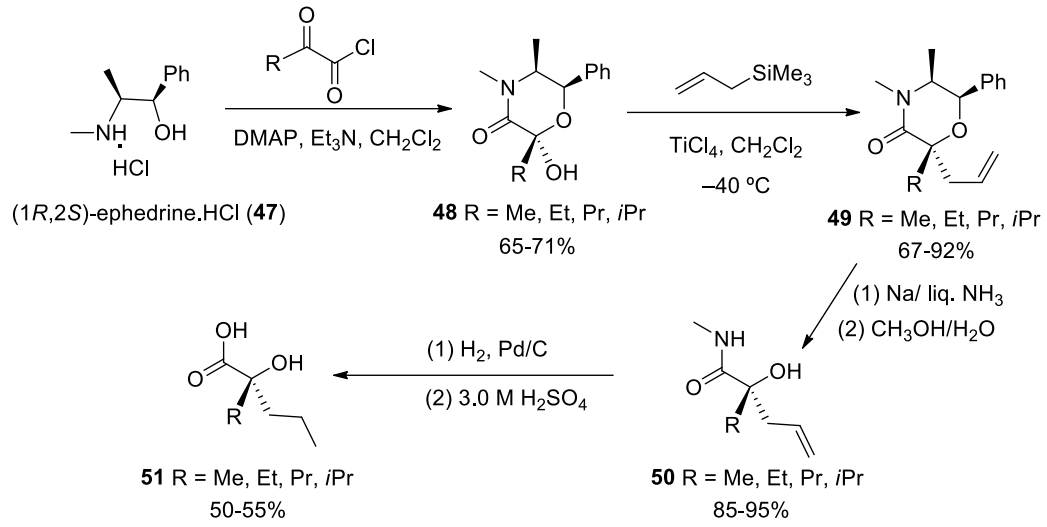


Figure 1.4. Strategy for the synthesis of functionalized quaternary stereocenters.

1.4 Previous work on ephedrine-derived morpholinones in the Pansare reseach group[5]

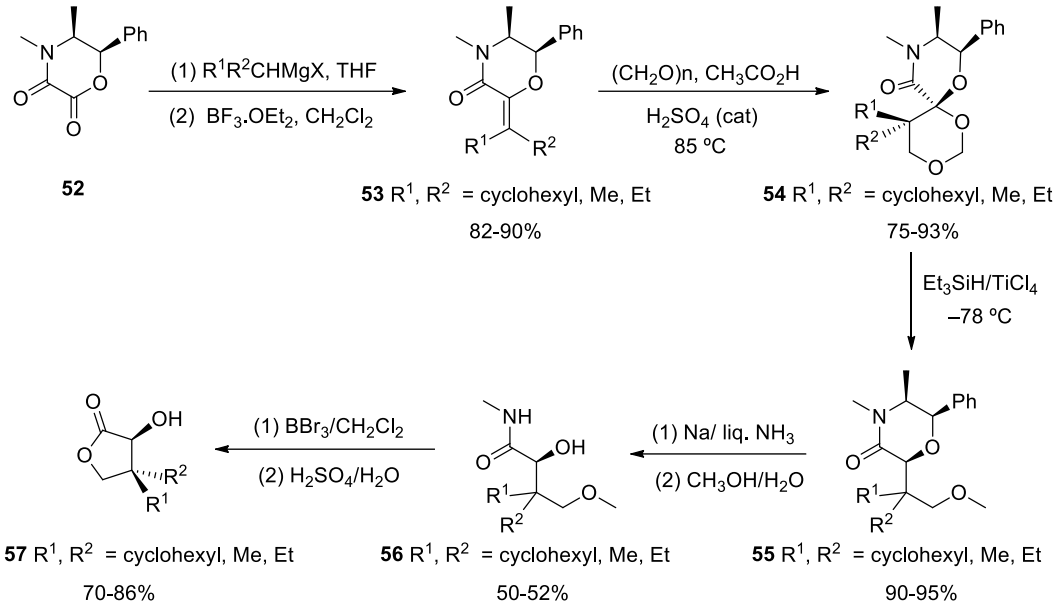
Since the work described in this chapter is conceptually based on previuos work conducted in the Pansare group, a brief discussion of the relevant prior studies is provided below.

In 1998, enantiomerically enriched α-hydroxy carboxylic acids[5a] **51** were synthesized from ephedrine-derived morpholinone hemiacetals by stereoselective allylation reactions (Scheme 1.08). (1*R*,2*S*)-Ephedrine hydrochloride (**47**) was subjected to acylations with aliphatic α-keto acid chlorides to give the corresponding hemiacetals **48**. Stereoselective allylation of **48** with allyltrimethylsilane/$TiCl_4$ provided **49** as single diastereomers. Removal of the ephedrine portion in **49** by dissolving metal reduction afforded the α-hydroxy amides **50**, which were then converted to known α-hydroxy carboxylic acids **51** by reduction of the double bond and hydrolysis of the amide.



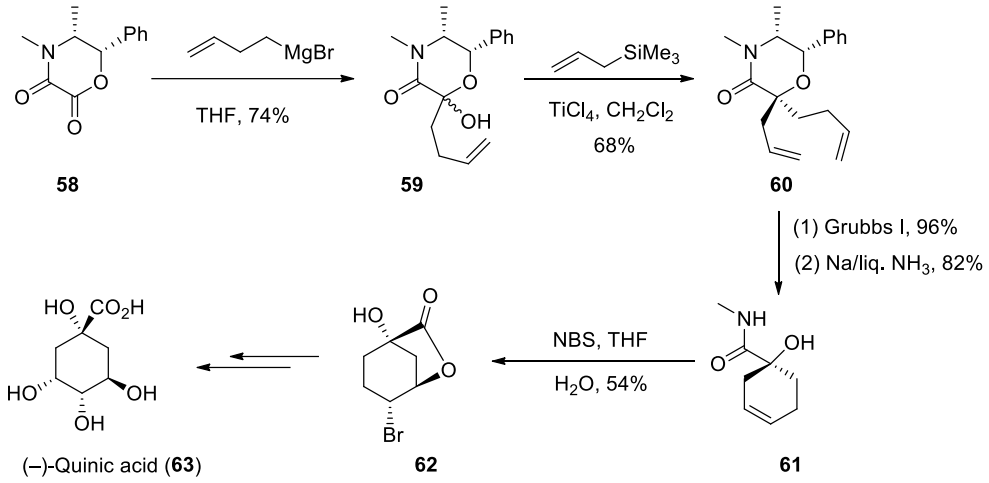
Scheme 1.08

In 2003, the Pansare group reported an efficient enantioselective method for the synthesis of analogues of pantolactone **57**[5b] (Scheme 1.09) from ephedrine-derived chiral alkylidene morpholinones by employing the Prins reaction as a key step. Dione **52** was treated with Grignard reagents to provide the corresponding hemiacetals, which were dehydrated to afford alkylidene morpholinone **53**. The Prins reaction of **53** gave spiromorpholinones **54** as single diastereomers. The opening of dioxane rings in **54** in the presence of $TiCl_4$/triethylsilane afforded **55**, which was subjected to dissolving metal reduction to provide the corresponding α-hydroxy amides **56**. The amides **56** were converted to analogues of pantolactone **57** by a one pot demethylation and acid-catalyzed lactonization protocol.



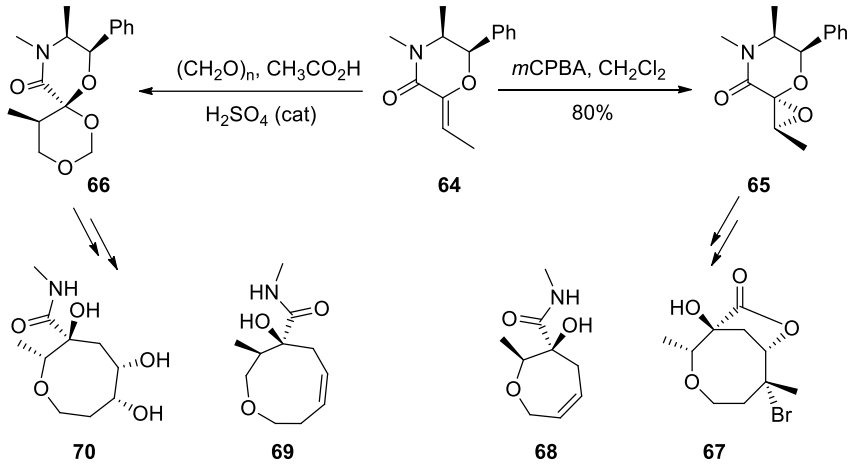
Scheme 1.09

In 2006, the enantiomerically enriched key precursor **62**[5c] of (–)-quinic acid (**63**) was synthesized from an ephedrine-derived morpholinedione **58** by stereoselective allylation and ring-closing metathesis as the key reactions (Scheme 1.10). Dione **58** was treated with the Grignard reagent derived from 4-bromobutene to give hemiacetal **59** which was subjected to an allylation reaction to provide **60** as a single diastereomer. Compound **60** was converted into the key precursor **62** in three steps, namely, ring-closing metathesis, dissolving metal reduction and bromolactonization.



Scheme 1.10

In the same year, the Pansare group also developed enantioselective routes to functionalized, seven-, eight-, and nine-membered oxacycles[5d] from ephedrine-derived methylidene morpholinone **64** (Scheme 1.11). Stereoselective epoxidation and Prins reaction of **64** provided **65** and **66** as single diastereomers respectively. The diastereoselective and regioselective transformations of **65** and **66** provided functionalized, seven-, eight-, and nine-membered oxacycles **67**-**70**.



Scheme 1.11

1.5 Results and Discussion

Two morpholinediones **52** and **71** were chosen as the synthetic precursors for the bromoalkylidene morpholinones **42** and **43** that were required for our studies. Commercially available (1*R*,2*S*)-ephedrine hydrochloride (**47**) was used to prepare **42**. The amino alcohol *S*-2-(methylamino)-1,1-diphenylpropanol (**74**), required for preparing **71**, was chosen as a potential alternative to ephedrine, which is a controlled drug precursor. In recent years, this has limited its availability for research in synthetic chemistry.

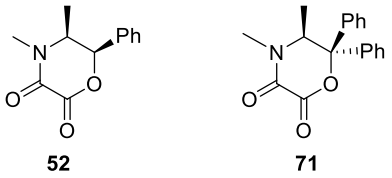
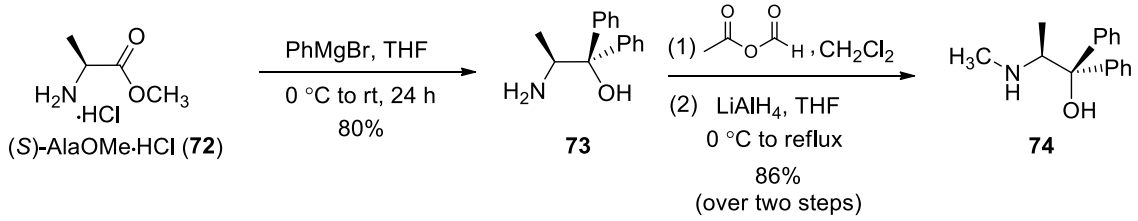


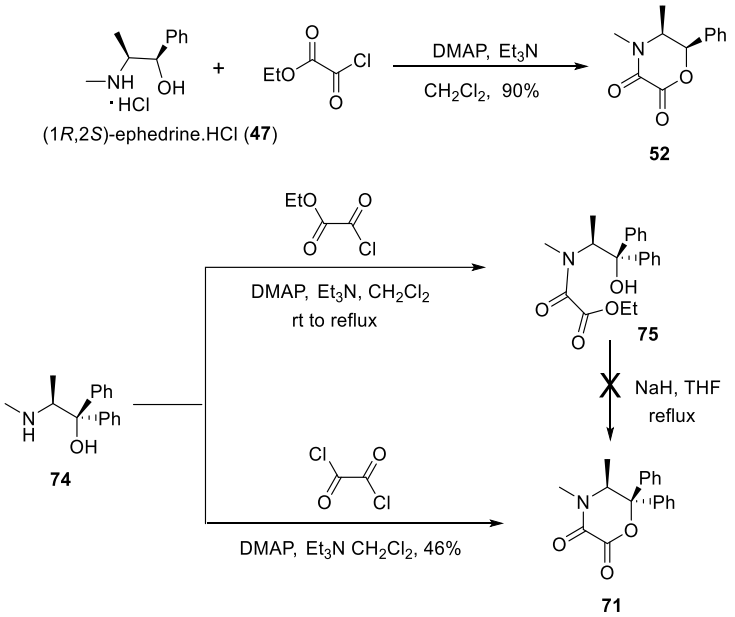
Figure 1.5 Morpholinediones **52** and **71.**

Amino alcohol **74** was synthesized from (*S*)-alanine methyl ester hydrochloride (**72**, Scheme 1.12) following the literature procedures.[6] Thus, the reaction of **72** with four equivalents of the phenylmagnesium bromide provided the tertiary alcohol **73**. *N*-Formylation of **73** using acetic formic anhydride followed by reduction of the formyl group, using $LiAlH_4$, furnished the required amino alcohol **74**.



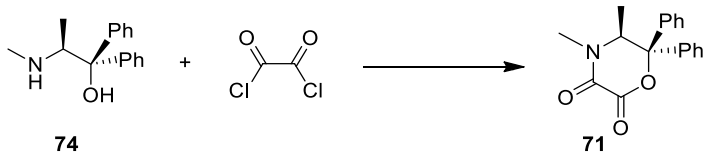
Scheme 1.12 Synthesis of amino alcohol **74**

With the amino alcohols **47** and **74** in hand, they were converted to the morpholinediones **52** and **71** by treatment with ethyl oxalyl chloride and oxalyl chloride respectively by employing the procedure previously developed in the Pansare group[5d,7] (Scheme 1.13). While this method (Et_3N as the base and CH_2Cl_2 as the solvent) works well for the reaction of 1*R*, 2*S*-ephedrine with ethyl oxalyl chloride for the synthesis of **52**, a similar reaction with **74** provided only the open chain amido-ester **75** (Scheme 1.13), which could not be cyclized to the required dione (NaH, THF, reflux). Although, the reaction of **74** with oxalyl chloride (Et_3N as the base and CH_2Cl_2 as the solvent) provided **71**, the yield was low (46%, Table 1.2, entry 1). Hence, an optimization study was conducted for the reaction of **74** and oxalyl chloride.



Scheme 1.13 Synthesis of morpholinediones **52** and **71**.

Table 1.1 Optimization of the synthesis of diphenylmorpholinedione **71**



74 **71**

Entry	Conditions	Yield[a]
1	Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 8 h	46%
2	Et_3N, DMAP, THF, 0 °C to rt, 10 h	57%
3	CH_3COOH, Et_3N, CH_2Cl_2, 0 °C to rt, 9 h	56%
4	CF_3COOH, CH_2Cl_2, 0 °C to rt, 20 h	>99%
5	CH_2Cl_2, 0 °C to rt, 12 h	75%

[a]isolated yields

Changing the reaction solvent to THF improved the yield of **71** to 57% (Table 1.1, entry 2). Since the formation of **71** was always accompanied by the formation of significant amounts of an intractable insoluble material, it was reasoned that polymerization of the initially formed *N*-acyl derivative **77** or **78** (Figure 1.6), as opposed to cyclization, was a potential issue. A reasonable solution to this problem would be the preferential formation of the *O*-acyl derivative **80** which should cyclize to provide the dione. With this objective in mind, amino alcohol **74** was first treated with one equivalent of acetic acid to make the ammonium acetate **79** (Figure 1.6) *in situ*. Subsequent addition of oxalyl chloride and then triethylamine provided **71** in slightly higher yield (56%, Table 1.2, entry 3). Surprisingly, formation of the dione **71** was observed in this reaction even before addition of the triethylamine. This suggested that the amine base was not necessary for the cyclization. Indeed, treatment of **74** with one equivalent of trifluoroacetic acid followed by the dropwise addition of oxalyl chloride furnished **71** in near-quantitative yield (>99%, Table 1.2, entry

4). The reasons for the high yield of **71** under these conditions is not clear at present. Interestingly, the reaction of **74** with oxalyl chloride in the absence of added base or acid also provided **71**, although in 75% yield (Table 1.2, entry 5).

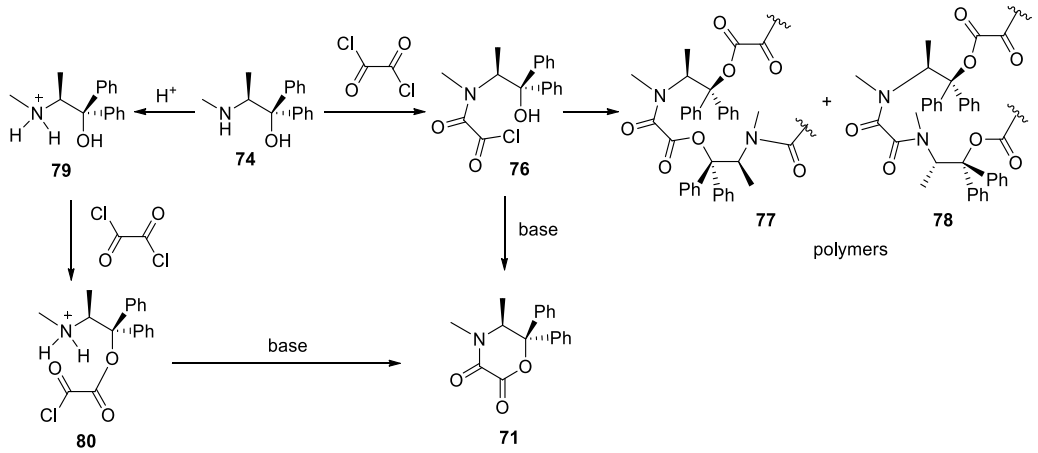
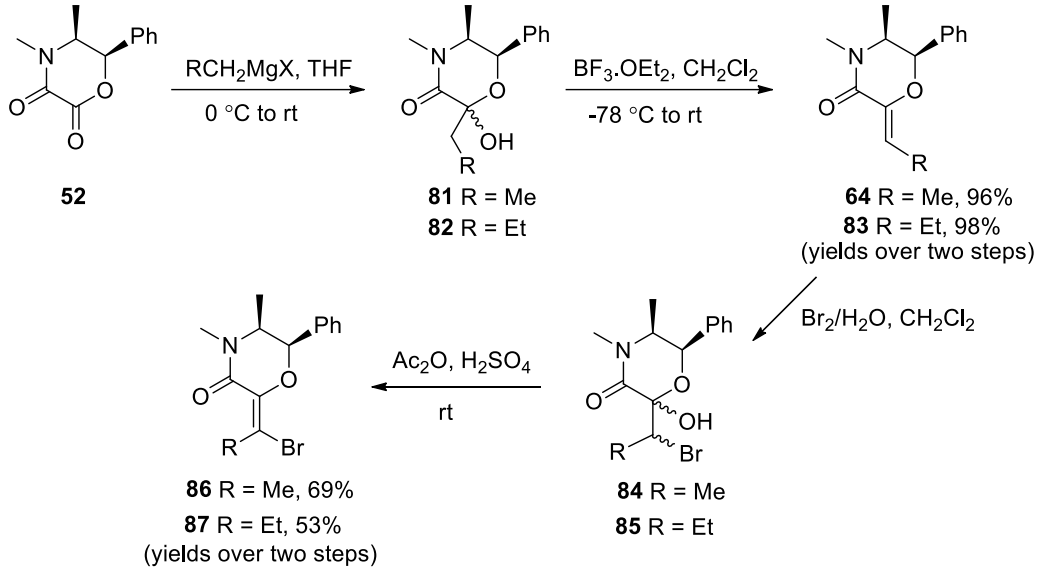


Figure 1.6

The above results are intriguing since they contradict conventional wisdom for *N*-acylation reactions, involving an acid chloride and an amine, which suggests that the addition of a base is necessary for neutralization of the acid generated during the reaction which would otherwise stop the acylation process by protonating the amine. The fact that the addition of trifluoroacetic acid actually increases the yield of **71** is, therefore, surprising.

Morpholinediones **52** and **71** were converted into bromoalkylidene morpholinones in a few steps. Treatment of **52** with ethylmagnesium bromide or propylmagnesium chloride provided the corresponding hemiacetals **81** and **82** which were dehydrated to furnish the alkylidene morpholinones **64**[7a] (96%) and **83**[7b] (98%, Scheme 1.14). These were converted to the key *Z*-bromoalkylidene morpholinones **86** and **87** respectively by conversion to the bromohemiacetals **84** and **85** (Br_2/H_2O) and subsequent dehydration.

Notably, under optimized conditions (Scheme 1.14), the corresponding *E*-isomers were generally not obtained.



Scheme 1.14 Synthesis of bromoalkylidene morpholinones **86** and **87**.

The *Z*-alkene geometry in **86** and **87** was assigned on the basis of anisotropic deshielding (^{1}H NMR) of the γ-hydrogens[8] in the embedded butenamide motif (CH_3 appears at δ 2.88 in **86** and the CH_2 appears at δ 3.33-3.12 in **87**, Figure 1.7) as compared to the corresponding *E*-isomers (CH_3 appears at δ 2.49 in (*E*)-**86** and the CH_2 appears at δ 2.90-2.67 in (*E*)-**87** respectively, Figure 1.7) which were occasionally obtained in trace amounts (<5%, (*E*)-**86** and (*E*)-**87**). A similar trend in the chemical shift of the characteristic C3-protons in isomerically pure prenyl derivatives **88** (Figure 1.7) is reported by Solladié.[8] In *Z*-**88**, the proton at C3 appears at δ 5.49, whereas in *E*-**88** it appears at δ 5.02. The deshielding of the proton at C3 in *Z*-**88** is attributed to anisotropic deshielding by the aldehyde carbonyl group.

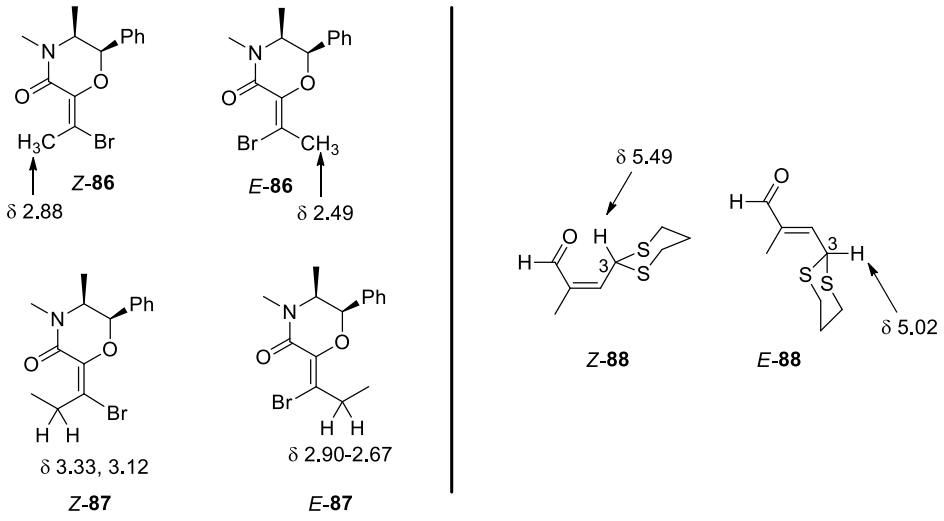
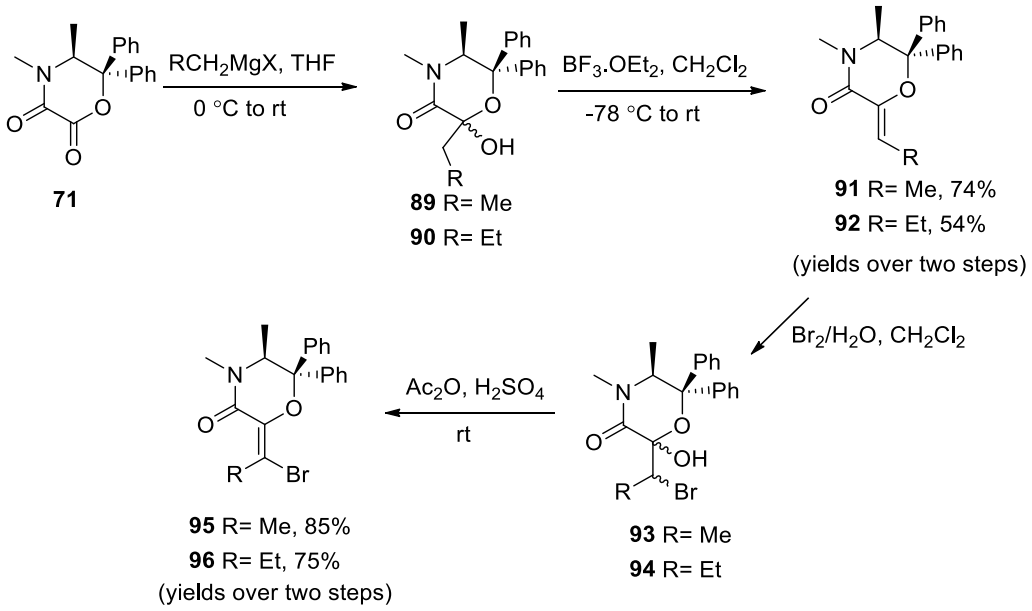


Figure 1.7 Chemical shifts of diagnostic protons in bromoalkylidene morpholinones and in prenyl derivatives.

The synthetic strategy in Scheme 1.14 was also utilized for the synthesis of (bromoalkylidene)morpholinones **95** and **96** (Scheme 1.15) from **71**. Treatment of **71** with ethylmagnesium bromide or propylmagnesium chloride provided the corresponding hemiacetals **89** and **90** which were dehydrated to furnish the alkylidenemorpholinones **91** (74%) and **92** (54%, Scheme 1.15). These were converted to the key (*Z*-bromoalkylidene)morpholinones **95** and **96** respectively by conversion to the bromohemiacetals **93** and **94** (Br_2/H_2O) and subsequent dehydration. Here, as well, the corresponding *E*-isomers were generally not obtained. As before, the *Z*-alkene geometry in **96** was assigned on the basis of anisotropic deshielding (^{1}H NMR) of the methylene group (appeared at δ 3.15)[8] in *Z*-**96** as compared to the corresponding *E*-**96** (methylene group appered at δ 2.97), which was obtained by dehydration of the bromohemiacetal **94** at 50 ^{o}C in ~5% yield.[9] The morpholinone (*E*)-**95** could not be obtained for comparison with **95**. However, since dehydration of the bromohemiacetal **94** obtained from **92** at ambient

temperature had provided **96** as the only isolable product, **95** was assigned the *Z*-geometry by analogy.

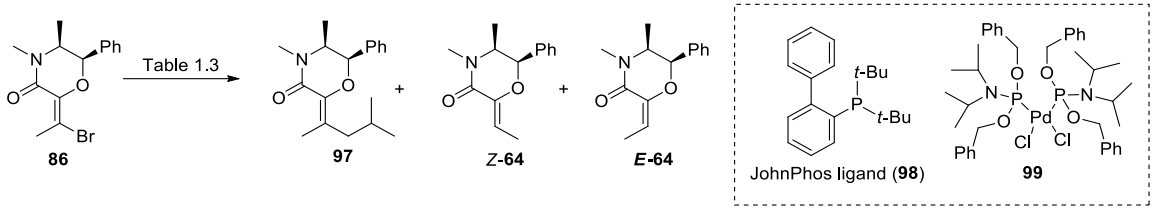


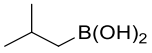
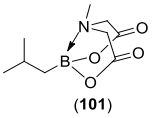
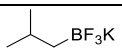
Scheme 1.15 Synthesis of bromoalkylidene morpholinones **95** and **96**.

At this stage, the morpholinones **86**, **87**, **95** and **96** possess one (methyl or ethyl) of three substituents that would eventually adorn the quaternary α-carbon in the target carboxylic acids or aldehydes. The next objective was the introduction of an additional substituent by cross-coupling of the vinyl bromide moiety in **86**, **87**, **95** and **96**. Clearly, the stereoselectivity of this C-C bond forming step was critical for the formation of a stereodefined (at the alkene) alkylidenemorpholinone. Initial attempts to introduce an alkyl substituent in **86** by the Negishi or Kumada cross-coupling[10] of alkylmetal reagents (alkylzinc bromides and alkylmagnesium halides) with the vinyl bromide were uniformly unsuccessful under a variety of conditions. These reactions either proceeded in very low yield or resulted in reduction of the vinyl bromide to the corresponding alkene. Attempted

Suzuki-Miyaura cross-couplings of **86** with alkylboronic acids[11a] **100** (Table 1.2, entries 1-6) or B-alkyl MIDA boronates[11b] **101** (Table 1.2, entries 7-9) were similarly unsuccessful. Fortunately, the use of potassium alkyl trifluorobrates[12] **102** as the cross-coupling partners provided the coupled product **97** (Table 1.2, entry 10) in 80% yield. The optimized conditions (Table 1.2, entry 10) were used in subsequent cross coupling reactions of **86** with various potassium alkyl trifluoroborates.

Table 1.2 Optimization of Suzuki-Miyaura cross-coupling reaction.



Entry	Organoborane	Catalyst	Conditions	Result
1[a]		**98**+$Pd(OAc)_2$	KF, THF, rt, 24 h, reflux, 30 h	NR
2		$Pd(PPh_3)_4$	K_2CO_3, DME, reflux, 4 h	*E*-**64** (30%)[b]
3	 (**100**)	$PdCl_2(dppf)_2$	K_2CO_3, DME, reflux, 6 h	**97**+*E*-**64**
4[a]		$Pd(OAc)_2$	K_2CO_3, DME, reflux, 8 h	NR
5[a]		**99**	Na_2CO_3, acetone/water (1:1), rt, 22 h, 50 °C, 13 h	NR
6[a]		**99**	Cs_2CO_3, CH_3CN, rt, 20 h, reflux, 6 h	NR
7		$PdCl_2(dppf)_2$	K_2CO_3, THF/H_2O (5:1), reflux, 43 h	*E*-**64**
8[a]	 (**101**)	**99**	Na_2CO_3, acetone/water (1:1), rt, 29 h, 70 °C, 8 h	NR
9		$Pd(PPh_3)_4$	Cs_2CO_3, CH_3CN, reflux, 52 h	**97**+*E*-**64**
10	 (**102**)	$PdCl_2(dppf)_2$	Cs_2CO_3, toluene, H_2O, 80 °C	**97** (80%)[b]

[a]**86** was recovered, [b]isolated yields, NR = no reaction

Suzuki-Miyaura cross-couplings of the morpholinones **86**, **87**, **95** and **96** with a variety of primary alkyl trifluoroborates were then examined. All alkyl trifluoroborates were successfully coupled with morpholinones **86**, **87**, **95** and **96** to give the corresponding cross-coupled products in good yields (Figure 1.8). With the exception of cyclopropyltrifluoroborate, secondary alkylboronic acids or secondary alkyl trifluoroborates did not furnish the expected cross-coupling products. However, cross-coupling reactions of **86**, **87** and **95** with arylboronic acids[10] proceeded smoothly and provided the corresponding alkyl/aryl substituted morpholinones (**97** and **103-114**, Figure 1.8).

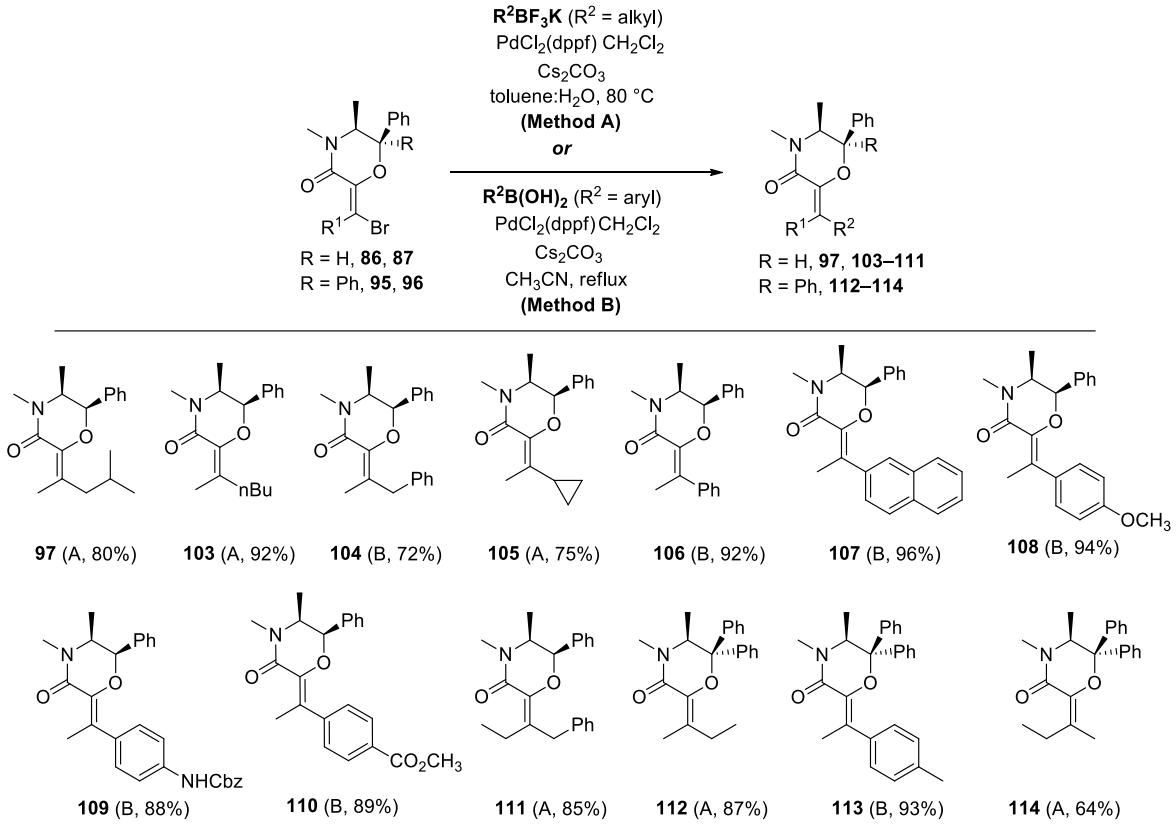
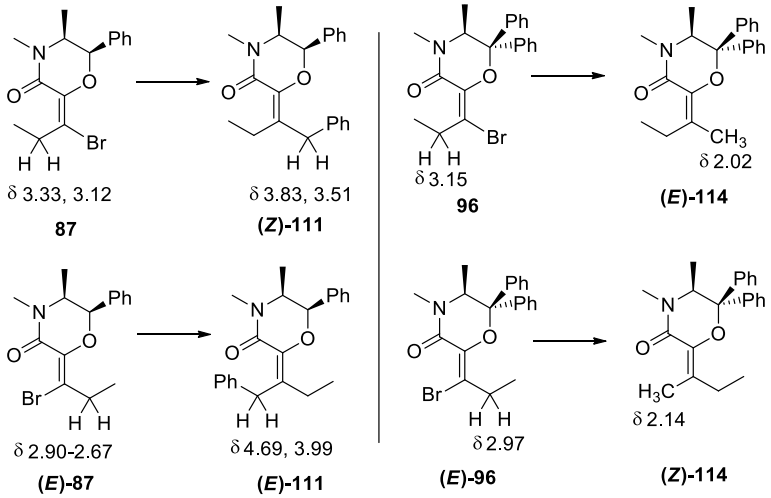


Figure 1.8 Suzuki-Miyaura cross-coupling of bromoalkylidene morpholinones.

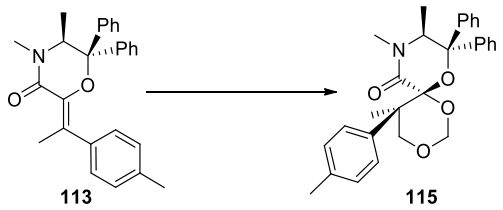
The stereoselectivity of the cross-coupling reaction was ascertained by the conversion of diastereomerically pure bromoalkenes to diastereomeric cross-coupling products. Thus, cross-coupling of bromoalkene **87** with potassium benzyltrifluoroborate provided the alkylidenemorpholinone (*Z*)-**111** whereas (*E*)-**87** gave the diastereomeric (*E*)-**111** (Scheme 1.16). Similarly, the cross-coupling of **96** with potassium methyltrifluoroborate provided (*E*)-**114**, but (*Z*)-**114** was obtained from a similar reaction of (*E*)-**96** (Scheme 1.16). Notably, the cross coupling of **95** with potassium ethyltrifluoroborate also provided (*Z*)-**114**. Since none of the diastereomeric cross-coupling product was detected (^{1}H NMR) in the reactions of **87**/(*E*)-**87** and **96**/(*E*)-**96**, all of the cross-coupling reactions of **86**, **87**, **95** and **96** were assumed to proceed with retention of configuration to provide the morpholinones **97** and **103**-**114**. As with the bromoalkenes, the stereochemical assignments for the cross-coupling products are based on the anisotropic deshielding of the γ-hydrogens in the alkene substituent that is *syn* to the morpholinone carbonyl group.[8]



Scheme 1.16 Diastereoselective cross-coupling reactions of bromoalkylidene morpholinones.

With the disubstituted alkylidenemorpholinones in hand, the stage was set for the final step in the construction of the quaternary stereocenter. To this effect, the alkylidenemorpholinone **113** was subjected to a Prins-type reaction[13] with paraformaldehyde or trioxane under various conditions (Table 1.3). Classical Prins reaction conditions (paraformaldehyde, acetic acid and conc. H_2SO_4) provided **115** in 48% yield from **113** (Table 1.3, entry 1). Conducting the reaction in TFA instead of acetic acid and avoiding the use of H_2SO_4 was beneficial, and **115** was obtained in 87% yield (Table 1.3, entry 7).

Table 1.3 Screening of Prins reaction conditions



S. No	Conditions	Product 115[a]
1	$(CH_2O)_n$, AcOH, Cat. H_2SO_4, 85 °C, 21 h	48%
2	$(CH_2O)_n$, AcOH, Cat. H_2SO_4, 55 °C, 54 h	46%
3[b]	$(CH_2O)_n$, AcOH, Cat. H_2SO_4, 85 °C, 2.5 h, MW	-
4[b]	$(CH_2O)_n$, $ZnCl_2$, THF, rt, 24 h, reflux, 24 h	NR
5[c]	1,3,5-trioxane, $ZnCl_2$, THF, rt, 48 h	NR
6[c]	1,3,5-trioxane, $TiCl_4$, THF, 0 °C to rt, 24 h	NR
7	$(CH_2O)_n$, TFA, rt , 5 days	87%

[a]isolated yields, [b]NMR of crude prod. is complex, [c]**113** was recovered, NR = no reaction

Depending on the substrate, these two methods were applied to a variety of alkylidenemorpholinones (Figure 1.9), one employing the more classical acetic acid/cat.

H_2SO_4 protocol with heating if necessary, and the other employing TFA as the solvent (at ambient temperature or at 0 ºC). Pleasingly, these reactions generated the spiromorpholinones **115-127** in good yield (Figure 1.9). The yield of **122**, from morpholinone **106**, is relatively low (32%) due to competing substitution on the aromatic ring. Notably, the Prins products were obtained as single diastereomers, the only exception being **127** which was obtained as a 5:1 mixture of diasteromers. In this case, purification provided diastereomerically pure **127** (71%). The reason for the moderate diastereoselectivity for **127** is not clear at present.

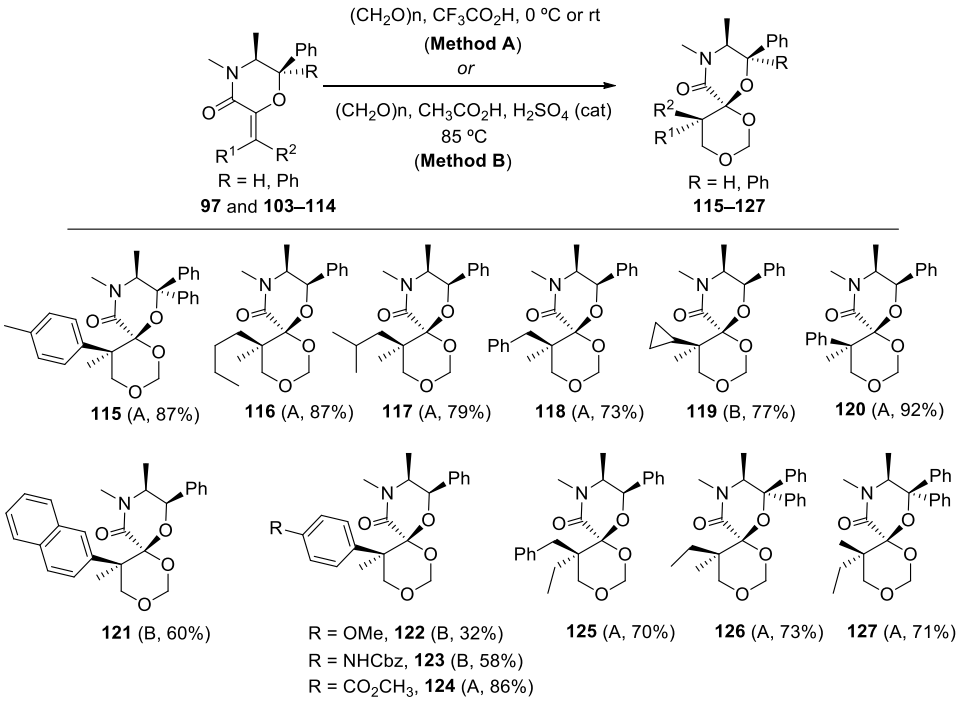


Figure 1.9 Prins reactions of alkylidenemorpholinones.

The stereochemistry at the newly-formed quaternary carbon and at the spiroacetal stereocenter in **115-127** are assigned by analogy to other reactions of the morpholinone template[6] which proceed from the less-substituted face of the morpholinone ring (Figure 1.10). We propose a mechanism for the Prins reaction in which formaldehyde adds from

the *Re*-face of **128** to generate the boat-like oxocarbenium ion **129**. Excess of formaldehyde reacts with primary alcohol in **129** to furnish hemiacetal **130**. Axial addition of the primary alcohol to the oxocarbenium ion provides the spiromorpholinones **131** as single diastereomers.

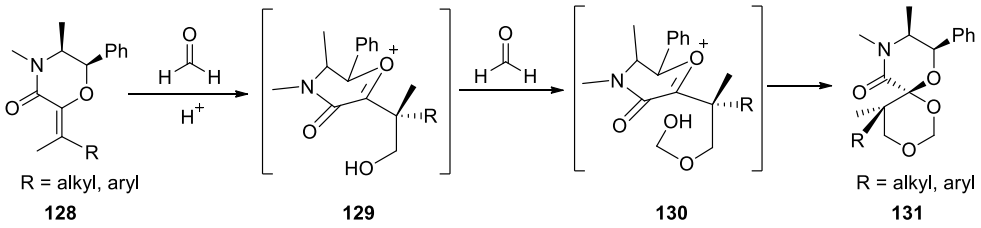
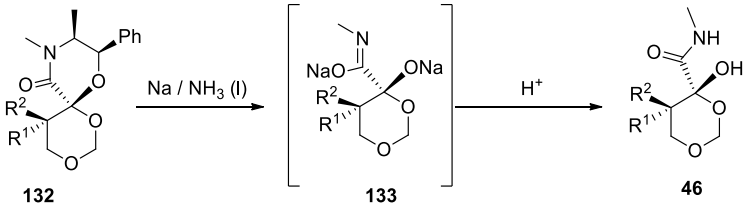


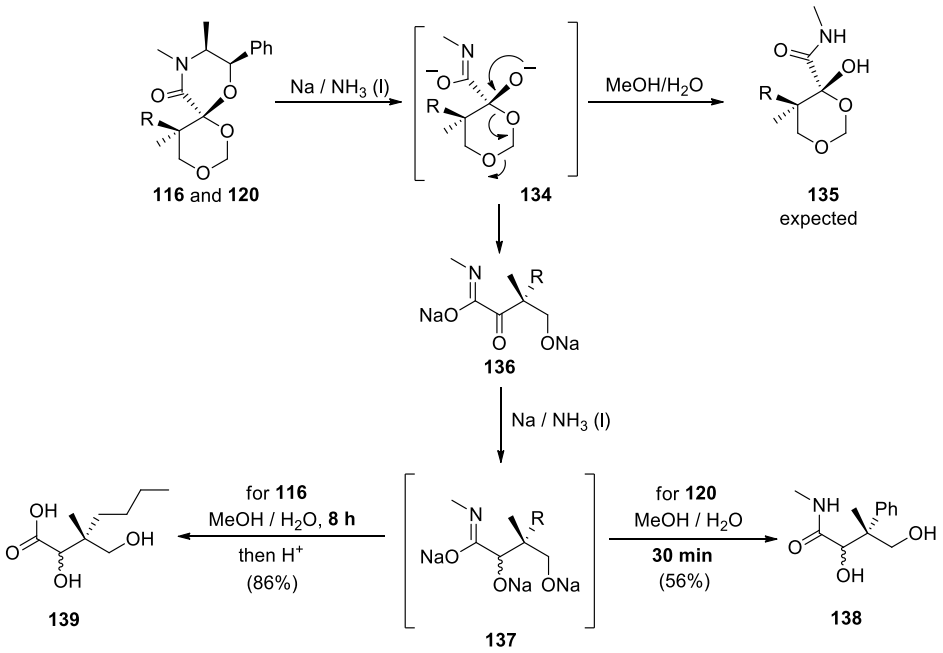
Figure 1.10 Plausible mechanism for Prins reaction.

Having constructed the quaternary stereocenter, we next examined the removal of the amino alcohol portion in the spiromorpholinones in order to liberate the functionalized quaternary-carbon bearing building blocks that were the objective of this study. Previous studies[6] on ephedrine-derived morpholinones had shown that dissolving metal reduction accomplishes cleavage of the benzylic C–O bond as well as the C–N bond β- to the phenyl group in the morpholinone. Hence, it was anticipated that a dissolving metal reduction of the spiromorpholinones prepared in this study would generate α-hydroxy amides based on the 1,3-dioxanyl scaffold (Scheme1.17).



Scheme 1.17 Dissolving metal reduction of ephedrine-derived morpholinones.

In initial studies, two representative spiromorpholinones, one with two alkyl groups at the quaternary carbon (**116**) and the other with an alkyl and an aryl substituent (**120**), were subjected to dissolving metal reduction (Na/NH_3). Unexpectedly, but pleasingly, the reduction of **120** provided the α,γ-dihydroxy amide **138** (56%) after quenching the reaction with MeOH/water followed by stirring at room temperature for 30 min (Scheme 1.18). Presumably, initial C-O and C-N bond cleavage in the morpholinone generates an intermediate which undergoes fragmentation of the dioxane ring to provide an α-keto amide which is reduced further to the dihydroxy amide **137**. Thus, four transformations are accomplished in one step. Notably, products arising from reduction of the phenyl ring on the dioxane portion in **120** were not observed. Futhermore, stirring the quenched ($MeOH/H_2O$) reaction mixture, obtained from **116**, at ambient temperature for 8 h directly provided the hydroxy acid **139** in good yield (86%, Scheme 1.18).



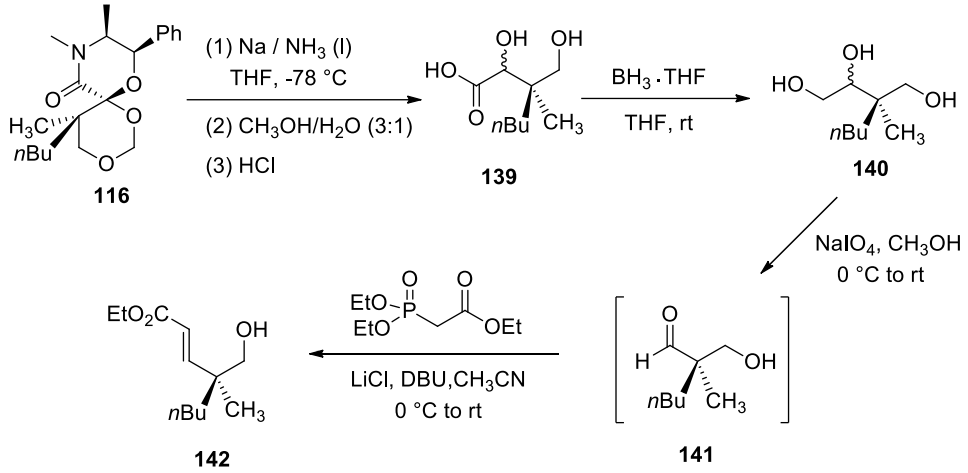
Scheme 1.18 Dissolving metal reduction of spiromorpholinones **116** and **120**.

Although the *in-situ* reduction of the α-keto amides is not diastereoselective (1:1 dr), it was expected that the α-stereocenter can be manipulated by oxidation of a suitably protected derivative to the ketone followed by diastereoselective reduction.[14] If required, the diastereomers of **138** and **139** can be easily separated by chromatography. α,γ-Dihydroxy acids and amides such as **139** and **138** are precursors of β,β-disubstituted-γ-butyrolactones that are analogs of pantolactone. Such lactones provide synthetic pantothenamides (*N*-modified α,γ-dihydroxy amides) by aminolysis.[15] Recent studies[16] have shown that the biological activity of pantothenamides depends on the substitution at, and the configuration of, the quaternary carbon. Notably, these key structural features can be controlled with the modular assembly of quaternary stereocenters described for **138** and **139**.

Determination of the absolute configuration of the quaternary carbon in the hydroxy acids required their conversion to known aldehydes or carboxylic acids for correlation. This conversion would also achieve the objective of preparing quaternary stereocenter-containing acyclic motifs that are amenable to functionalization. Hence, in order to demonstrate the generality of the amino alcohol removal and conversion of the α-hydroxy acid products into the targets, selected spiromorpholinones derived either from 1*R*,2*S*-ephedrine or from *S*-2-(methylamino)-1,1-diphenylpropanol, both bearing alkyl, aryl or arylalkyl substituents were converted into functionalized, quaternary stereocenter-containing building blocks (Schemes 1.19 and 1.120).

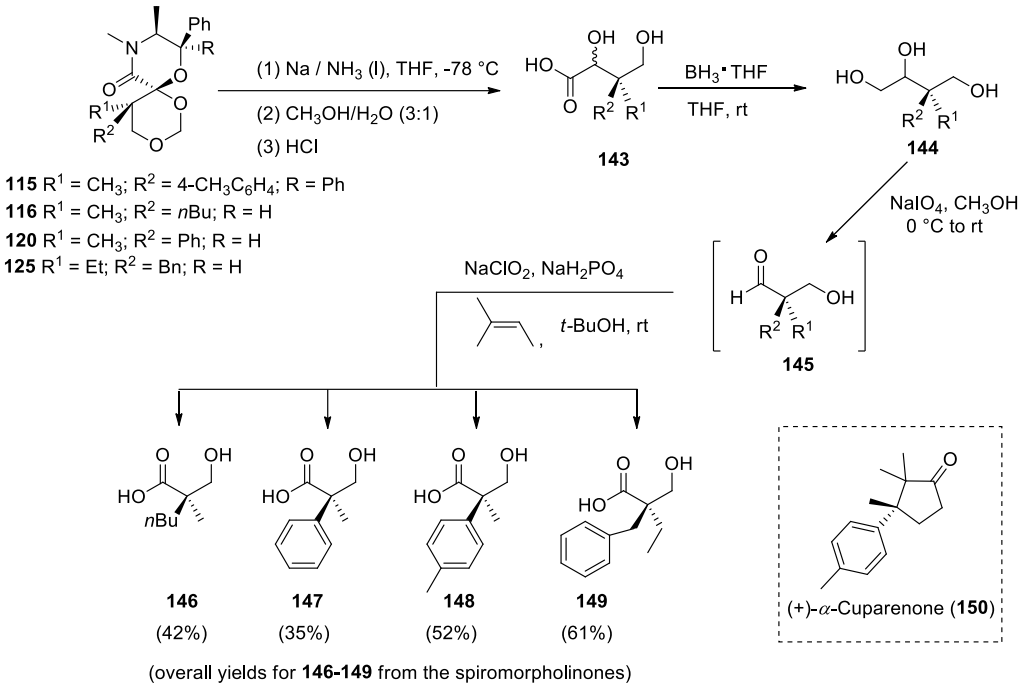
The crude carboxylic acid **139** obtained from the dissolving metal reduction of the spiromorpholinone **116** was subjected to a two-step protocol involving reduction with

borane followed by oxidative cleavage of the resulting vicinal diol **140** to aldehyde **141**. Aldehyde **141** was directly employed in a Horner-Wadsworth-Emmons (HWE) reaction to provide **142** (Scheme 1.19).



Scheme 1.19 Conversion of spiromorpholinone **116** to α,β-unsaturated ester **142**.

Similarly, selected spiromorpholinones were converted to corresponding hydroxy carboxylic acids **146-149** (Scheme 1.20). Spiromorpholinones **115**, **116**, **120** and **125** were subjected to dissolving metal reduction to provide respective dihydroxy carboxylic acids **143**, which were transformed into corresponding aldehydes **145** by borane reduction followed by oxidative cleavage of vicinal diols **144**. Pinnick oxidation of aldehydes **145** furnished corresponding β-hydroxy carboxylic acids **146-149** respectively (Scheme 1.20). Comparison of the optical rotations of the acids **147**[17] and **148**[18] with reported values confirmed the '*R*' configurations. The formation of the *'R*' enantiomers also confirms the stereochemical outcomes of the Prins reaction. The configurations of **142**, **146** and **149** are assigned by analogy.



Scheme 1.20 Conversion of spiromorpholinones to *β*-hydroxy carboxylic acids.

Notably, the methyl ester of the hydroxy acid **148** prepared in this study serves as a key starting material in the synthesis of (+)-*α*-cuparenone (**150**),[18] a quaternary stereocenter containing sesquiterpene. We anticipate that the other spiromorpholinones prepared in this study will also provide quaternary stereocenter-containing hydroxy aldehydes or carboxylic acids by employing a protocol similar to the ones described in Schemes1.19 and 1.20.

1.6 Conclusion:

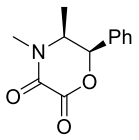
In conclusion, a modular synthesis of functionalized quaternary carbon containing building blocks has been developed. The procedure involves sequential, stereoselective C-C bond-forming reactions on chiral amino alcohol-derived alkylidene morpholinones. The methodology has the potential to rapidly assemble a variety of quaternary carbons that are adorned with a selection of alkyl and aryl substituents. This study has also identified *S*-2-(methylamino)-1,1-diphenylpropanol as a potential replacement for 1*R*,2*S*-ephedrine in the morpholinone template-based methodology.

1.7 Experimental section

General:

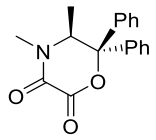
All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 and THF were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system. High-resolution mass spectra (EI or ESI) were obtained on a Waters GCT Premier Micromass mass spectrometer. Optical rotations were measured at the sodium D line on a JASCO-DIP 370 digital polarimeter at ambient temperature.

(5*S*,6*R*)-4,5-dimethyl-6-phenylmorpholine-2,3-dione(52):[7b]



Prepared from 1*R*,2*S* ephedrine hydrochloride (**47**) and ethyloxalyl chloride according to the literature procedure. Spectroscopic data for **52** was identical to the reported data.[7b]

(*S*)-4,5-Dimethyl-6,6-diphenylmorpholin-2,3-dione (71):

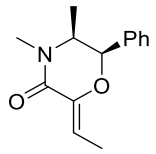


To a solution of (*S*)-2-(methylamino)-1,1-diphenylpropan-1-ol (**74**)[6] (100 mg, 0.410 mmol) in THF (12 mL) were added DMAP (5.0 mg, 0.041 mmol) and triethylamine (0.230 mL, 1.65 mmol) followed by dropwise addition of oxalyl chloride (53 µL, 0.62 mmol) at 0 ºC. The mixture was stirred at 0 ºC for 1 h and then at ambient temperature for 10 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with HCl (0.1 M, 2 x 5 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a black solid. Purification of the crude product by flash chromatography on silica gel (hexane/EOAc, 55:45) provide 75 mg (61%) of **71** as light brown solid. R_f = 0.24 (hexanes/EtOAc, 1:1); mp: 135.3-137.6 °C; $[\alpha]_D^{20}$ = – 325.7 (c 1, CH_2Cl_2); IR (neat): 2297, 1763, 1681, 1495, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44-7.27 (m, 10H, Ar*H*), 4.47 (q, 1H, *J* = 7.5 Hz, C*H*CH_3), 3.15 (s, 3H, NC*H*$_3$), 1.22 (d, 3H, *J* = 7.5 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4 (O*C*O), 153.3 (N*C*O), 141.4 (Ar*C*$_{ipso}$), 139.5 (Ar*C*$_{ipso}$), 129.3 (Ar*C*), 128.9 (Ar*C*), 128.7 (Ar*C*), 128.1 (Ar*C*), 125.4 (Ar*C*), 124.6 (Ar*C*), 87.0 (*C*CH), 59.0 (*C*HCH$_3$), 33.9 (N*C*H$_3$), 15.0 (*C*H$_3$); MS (APCI): 296.1 $(M+H)^+$; HRMS (CI): *m/z* 296.1280 (296.1287 calc. for $C_{18}H_{18}NO_3$, $(M+H)^+$).

General procedure for the synthesis of alkylidene morpholinones 64, 83, 91 and 92:[7a]

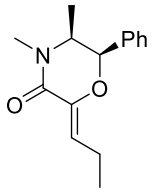
To suspension of the morpholinedione **52**[7b] or **71** in THF was added the appropriate alkylmagnesium halide at 0 °C and the mixture was stirred at ambient temperature. A aqueous saturated NH_4Cl solution was added, the mixture was extracted with ethyl acetate to provide the product hemiacetal, which was then used in the next step without purification. To a solution of the crude hemiacetal in CH_2Cl_2 was added $BF_3.OEt_2$ at -78 °C and the solution was stirred at ambient temperature for 14 h. It was then cooled to 0 °C and water was added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to provide the alkylidene morpholinone.

(*S*,*E*)-2-Ethylidene-4,5-dimethyl-6-phenylmorpholin-3-one (64):[7a,5a]



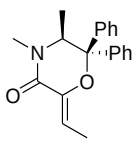
Prepared according to the general procedure. Reaction (*S*)-4,5-dimethyl-6-phenylmorpholin-2,3-dione **52** (4.50 g, 20.5 mmol) and ethylmagnesium bromide (8.21 mL, 24.6 mmol, 3.00 M in diethylether) provided 5.03 g (99%) of the hemiacetal 5*S*-2-ethyl-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (**51**) as a white foam (dr = 6.6:1). Dehydration of the hemiacetal in CH_2Cl_2 (30 mL) with $BF_3.OEt_2$ (7.73 mL, 61.6 mmol) provided 4.54 g (96% over two steps) of **64** as a pale-yellow gum. This was used in the next step without purification. Spectroscopic data for **64** was identical to the reported data.[7b]

(*S*,*E*)-2-Propylidene-4,5-dimethyl-6-phenylmorpholin-3-one (83):[5a]



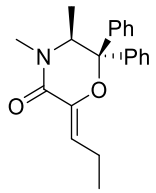
Prepared according to the general procedure. Reaction (*S*)-4,5-dimethyl-6-phenylmorpholin-2,3-dione **52** (1.00 g, 4.56 mmol) and propylmagnesium chloride (3.42 mL, 6.84 mmol, 2.00 M in diethylether) provided 1.90 g (99%) of the hemiacetal 5*S*-2-propyl-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (**82**) as a pale yellow solid (dr = 10:1) Dehydration of the hemiacetal in CH_2Cl_2 (15 mL) with $BF_3.OEt_2$ (1.71 mL, 13.7 mmol) to provided the pure alkylidene morpholinone without purification 1.08 g (98% over two steps) of **83** as a yellow gum. Spectroscopic data for **83** was identical to the reported data.[5a] R_f = 0.29 (EtOAc/hexanes, 2:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.29 (m, 5H, Ar*H*), 6.06 (t, 1H, *J* = 7.5 Hz, C=C*H*), 5.21 (d, 3 1H, *J* = 2.7 Hz, PhC*H*), 3.54 (dq, 1H, *J* = 6.6, 2.7 Hz, C*H*CH_3), 3.08 (s, 3H, NCH_3), 2.27 (quint., 1H, *J* = 7.5 Hz, CH_3CH_2), 1.05 (t, 3H, *J* = 7.5 Hz, C=CCH_2CH_3), 1.08 (d, 3H, *J* = 6.6 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8 (N*C*=O), 143.5 (ArC_{ipso} or *C*-C=O), 137.2 (ArC_{ipso} or *C*-C=O), 128.5 (2 × Ar*C*), 127.9 (Ar*C*), 125.5 (2 × Ar*C*), 118.5 (C=*C*H), 77.0 (Ph*C*H), 58.6 (*C*HCH_3), 33.6 (N*C*H_3), 18.3 (C=C*C*H_2CH_3), 13.5 (C=CCH_2*C*H_3), 11.7 (CH*C*H_3).

(*S*,*E*)-2-Ethylidene-4,5-dimethyl-6,6-diphenylmorpholin-3-one (91):



This was prepared according to the general procedure. Reaction of the dione **71** (1.00 g, 3.38 mmol) in anhydrous THF (10 mL) with ethylmagnesium bromide (4.06 mL, 4.06 mmol, 1.00 M in THF) provided 1.01 g (99%) of the hemiacetal (*S*)-2-ethyl-2-hydroxy-4,5-dimethyl-6,6-diphenylmorpholin-3-one (**89**) as a white solid (dr = 4.5:1). Dehydration of the hemiacetal **89** in CH_2Cl_2 (10 mL) with $BF_3.OEt_2$ (1.270 mL, 10.14 mmol) provided the crude alkylidene morpholinone. This was purified by flash chromatography on silica gel (hexanes/EtOAc, 7:3) to provide 767 mg (74% over two steps) of **91** as a white solid. R_f = 0.30 (EtOAc/hexanes, 1:1); mp: 138.7-140.1 °C; $[\alpha]_D^{20}$ = – 270.5 (c 1, CH_2Cl_2); IR (neat): 3066, 2982, 2932, 1619, 1480, 1450, 1401, 1325, 1152, 1071, 1040, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.39 (m, 2H, Ar*H*),7.36-7.05 (m, 8H, Ar*H*), 6.06 (q, 1H, *J* = 7.2 Hz, C=C*H*), 4.32 (q, 1H, *J* = 6.4 Hz, C*H*CH_3), 3.07 (s, 3H, NC*H*$_3$), 1.91 (d, 3H, *J* = 7.2 Hz, C=CHC*H*$_3$), 1.08 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5 (N*C*=O), 142.9 (Ar*C*$_{ipso}$ or *C*-*C*=O), 142.3 (Ar*C*$_{ipso}$ or *C*-C=O), 142.1 (Ar*C*$_{ipso}$ or *C*-C=O), 128.7 (2 × Ar*C*), 128.4 (2 × Ar*C*), 127.6 (Ar*C*), 127.1 (Ar*C*), 126.0 (2 × Ar*C*), 124.9 (2 × Ar*C*), 112.7 (C=*C*H), 81.9 (Ph_2C), 58.4 (*C*HCH_3), 33.7 (N-*C*H$_3$), 14.5 (=C*C*H$_3$), 10.6 (CH*C*H$_3$); MS (EI, pos.): *m*/*z* 308.2 $(M+H)^+$; HRMS (EI, pos.): *m*/*z* 307.1571 (307.1572 calc. for $C_{20}H_{21}NO_2$ (M^+)).

(*S*,*Z*)-4,5-Dimethyl-6,6-diphenyl-2-propylidenemorpholin-3-one (92):



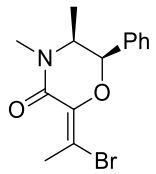
This was prepared according to the general procedure. Reaction of the dione **71** (1.00 g, 3.38 mmol) in anhydrous THF (10 mL) with propylmagnesium bromide (2.53 mL of a 2.00 M soln. in ether, 5.06 mmol) provided 1.02 g (89%) of the hemiacetal (*S*)-2-proyl-2-hydroxy-4,5-dimethyl-6,6-diphenylmorpholin-3-one (**90**) as a white solid (dr = 5.6:1). Dehydration of the hemiacetal **90** in CH_2Cl_2 (12 mL) with $BF_3.OEt_2$ (1.27 mL, 10.1 mmol) provided the crude alkylidene morpholinone. This was purified by flash chromatography on silica gel (hexanes/EtOAc, 7:3) to provide 583 mg (54% over two steps) of **92** as a white solid. R_f = 0.36 (CH_2Cl_2/EtOAc, 1:1); mp: 122.2-124.0 °C; $[\alpha]_D^{20}$ = – 209.9 (c 0.76, CH_2Cl_2); IR (neat): 2968, 2931, 1624, 1489, 1450, 1400, 1337, 1318, 1174, 1158, 1072, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.38 (m, 2H, Ar*H*), 7.36-7.26 (m, 6H, Ar*H*), 7.24-7.14 (m, 2H, Ar*H*), 6.01 (t, 1H, *J* = 7.5 Hz, C=C*H*), 4.32 (q, 1H, *J* = 6.4 Hz, C*H*CH_3), 3.07 (s, 3H, NC*H*$_3$), 2.43 (quint., 2H, *J* = 7.5 Hz, C=CC*H*$_2$$CH_3$), 1.10 (t, 3H, *J* = 7.5 Hz, C=CCH_2C*H*$_3$), 1.08 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7 (N*C*=O), 142.3 (ArC_{ipso}), 142.1 (ArC_{ipso}), 141.6 (*C*-C=O), 128.7 (2 × Ar*C*), 128.4 (2 × Ar*C*), 127.6 (Ar*C*), 127.1 (Ar*C*), 126.1 (2 × Ar*C*), 124.9 (2 × Ar*C*), 119.6 (C=*C*H), 81.9 (*C*Ph_2), 58.3 (*C*HCH_3), 33.8 (NC*H*$_3$), 18.6 (C=C*C*H$_2$$CH_3$), 14.5 (C=$CCH_2$*C*H$_3$), 13.4 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 322.2 $(M+H)^+$; HRMS (EI, pos.): *m*/*z* 321.1742 (321.1729 calc. for $C_{21}H_{23}NO_2$ (M^+)).

General procedure for the synthesis of bromoalkylidene morpholinones 86, 87, 95 and 96:

To a solution of the alkene in CH_2Cl_2 at room temperature was added a solution of bromine in water. The mixture was stirred for 3 h at room temperature and then extracted with CH_2Cl_2. The combined organic layers were washed with aqueous 5% $Na_2S_2O_3$, brine,

dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude bromohemiacetal this was dissolved in acetic anhydride and conc. H_2SO_4 (specified amount) was added to the solution. The mixture was stirred at room temperature and the acetic anhydride was removed under reduced pressure. The residue was cooled to 0 °C and basified with aqueous NaOH (10%). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

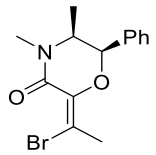
(5*S*,6*R*,*Z*)-2-(1-Bromoethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (86):



This was prepared according to the general procedure. Reaction of the alkene **64** (2.50 g, 10.8 mmol) in CH_2Cl_2 (20 mL) at room temperature with bromine (6.50 mL of a 2.00 M soln. in H_2O, 13.0 mmol) provided 3.43 g of the crude bromohemiacetal. This was dehydrated in acetic anhydride (10 mL) and conc. H_2SO_4 (0.25 mL) for 48 h to provide, after flash chromatography on silica gel (hexane/EtOAc, 7:3), 2.30 g (69% over two steps) of **86** as a pale-yellow gum. R_f = 0.29 (hexanes/EtOAc, 6:4); $[\alpha]_D^{20}$ = – 194.8 (c 0.86, CH_2Cl_2); IR (neat): 1660, 1610, 1441, 1389, 1284, 1212, 1151, 1065, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.39 (m, 4H, Ar*H*), 7.36-7.32 (m, 1H, Ar*H*), 5.28 (d, 1H, *J* = 2.8 Hz, PhC*H*), 3.60 (dq, 1H, *J* = 6.5, 2.8 Hz, C*H*CH_3), 3.08 (s, 3H, NCH_3), 2.88 (s, 3H, C=CH_3), 0.99 (d, 3H, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5 (*C*=O), 140.2 (*C*-C=O), 136.4 (Ar*C*), 128.5 (2 x Ar*C*), 128.0 (Ar*C*), 125.5 (2 x Ar*C*),

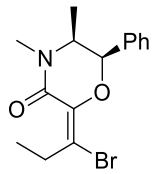
117.2(C=*C*Br), 77.02 (Ph-*C*), 58.8 (N*C*H), 33.6 (N*C*H_3), 24.9 (C=*C*H_3), 11.9 (CH*C*H_3); MS (EI, pos.): *m*/*z* 310.1 (M+1(^{79}Br))$^+$ and 312.1 (M+1(^{81}Br))$^+$; HRMS (CI): *m*/*z* 310.0436 (310.0443 calc. for $C_{14}H_{17}{}^{79}BrNO_2$ (M+H)$^+$) and 312.0423 (312.0422 calc. for $C_{14}H_{17}{}^{81}BrNO_2$ (M+H)$^+$).

(5*S*,6*R*,*E*)-2-(1-Bromoethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (*E*-86):



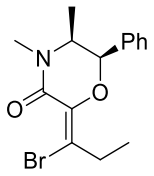
In some experiments, dehydration of the bromohemiacetal obtained from **64** provided a mixture of **86** and ***E*-86** which was separated by flash chromatography on silica gel (hexanes/EtOAc, 7:3) to provide ***E*-86** (2-4%) as a gum. R_f = 0.27 (hexanes/EtOAc, 6:4); $[\alpha]_D^{20}$ = – 140.3 (c 0.9, CH_2Cl_2); IR (neat): 2979, 2917, 1657, 1610, 1440, 1396, 1377, 1283, 1265, 1212, 1188, 1142, 1101, 1063, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.32 (m, 5H, Ar*H*), 5.24 (d, 1H, *J* = 2.8 Hz, PhC*H*), 3.60 (dq, 1H, *J* = 2.8, 6.5 Hz, NC*H*), 3.09 (s, 3H, NCH_3), 2.49 (s, 3H, C=CH_3), 0.99 (d, 3H, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 (*C*=O), 140.5 (*C*-C=O), 136.6 (ArC_{ipso}), 128.6 (2 x Ar*C*), 128.1 (Ar*C*), 125.3 (2 x Ar*C*), 110.8 (C=*C*Br), 77.5 (Ph-*C*), 59.0 (*C*HCH$_3$), 33.8 (N*C*H$_3$), 24.7 (H$_3$*C*C=C), 11.9 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 310.1(M+1(^{79}Br))$^+$ and 312.0 (M+1(^{81}Br))$^+$; HRMS (CI): *m*/*z* 309.0377 (309.0364 calc. for $C_{14}H_{16}{}^{79}BrNO_2$ (M$^+$)) and 312.0430 (312.0422 calc. for $C_{14}H_{17}{}^{81}BrNO_2$ (M+H)$^+$).

(5*S*,6*R*,*Z*)-2-(1-Bromopropylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (87):



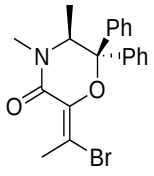
This was prepared according to the general procedure. Reaction of the alkene **83** (1.10 g, 4.48 mmol) in CH_2Cl_2 (10 mL) at room temperature with bromine in water (5.38 mL of a 1.00 M soln. in H_2O, 5.38 mmol) provided 1.40 g (4.10 mmol) of the crude bromohemiacetal as a white foam. This was dehydrated in acetic anhydride (10 mL) and conc. H_2SO_4 (0.5 mL) for 23 h to provide, after flash chromatography on silica gel (hexanes/EtOAc, 3:1), 713 mg (53% over two steps) of **87** as a brown gum. R_f = 0.47 (EtOAc/hexanes, 1:1); $[\alpha]_D^{20}$ = – 161.3 (c 1.7, CH_2Cl_2); IR (neat): 2975, 2933, 2875, 1656, 1606, 1449, 1398, 1380, 1287, 1266, 1214, 1191, 1152, 1062, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.28 (m, 5H, Ar*H*), 5.25 (d, 1H, *J* = 2.6 Hz, C*H*Ph), 3.58 (dq, 1H, *J* = 6.6, 2.7 Hz, C*H*CH_3), 3.33 (ABX_3, 1H, J_{AB} = 14.4 Hz, J_{AX} = J_{BX} = 7.2 Hz, C*H*$_2$$CH_3$), 3.12 ($ABX_3$, 1H, J_{AB} = 14.4 Hz, J_{AX} = J_{BX} = 7.2 Hz, C*H*$_2$$CH_3$), 3.08 (s, 3H, NC*H*$_3$), 1.21 (t, 3H, *J* = 7.2 Hz, CH_2C*H*$_3$), 0.97 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 (N*C*=O), 139.7 (ArC_{ipso} or *C*-C=O), 136.4 (ArC_{ipso} or *C*-C=O), 128.5 (2 × Ar*C*), 128.0 (Ar*C*), 125.4 (2 × Ar*C*), 125.0 (C=*C*CH_2), 77.6 (Ph*C*), 58.7 (*C*HCH_3), 33.6 (N-*C*H_3), 30.4 (*C*$H_2$$CH_3$), 13.8 (CH*C*$H_3$), 11.8 ($CH_2$*C*$H_3$); MS (APCI, pos.): *m*/*z* 324.1 $(M+1(^{79}Br))^+$ and 326.1 $(M+1(^{81}Br))^+$; HRMS (APPI, pos.): *m*/*z* 323.0513 (323.0521 calc. for $C_{15}H_{18}{}^{79}BrNO_2$ (M^+)) and 326.0567 (326.0579 calc. for $C_{15}H_{18}{}^{81}BrNO_2$ $(M+H)^+$).

(5*S*,6*R*,*E*)-2-(1-Bromopropylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (*E*-87):



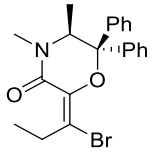
In some experiments, dehydration of the bromohemiacetal obtained from **83** provided a mixture of **87** and ***E*-87** which was separated by flash chromatography on silica gel (hexanes/EtOAc, 3:1) to provide ***E*-87** in (3-5%) yield as a pale-yellow solid. R_f = 0.39 (EtOAc/hexanes, 1:1); mp: 90.9-92.1 °C; $[\alpha]_D^{20}$ = –151.6 (c 0.8, CH_2Cl_2); IR (neat): 2970, 2930, 2871, 1650, 1605, 1455, 1444, 1394, 1378, 1287, 1256, 1187, 1140, 1107, 1063, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.30 (m, 5H, Ar*H*), 5.23 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 3.58 (dq, 1H, *J* = 6.6, 2.7 Hz, C*H*CH_3), 3.09 (s, 3H, NC*H*$_3$), 2.90-2.67 (m, 2H, C*H*$_2$$CH_3$), 1.16 (t, 3H, *J* = 7.4 Hz, CH_2C*H*$_3$), 0.99 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3 (N*C*=O), 139.9 (Ar*C*$_{ipso}$ or *C*-C=O), 136.6 (Ar*C*$_{ipso}$ or *C*-C=O), 128.6 (2 × Ar*C*), 128.1 (Ar*C*), 125.3 (2 × Ar*C*), 118.4 (C=*C*CH_2), 77.6 (Ph*C*), 59.0 (*C*HCH_3), 33.9 (N-*C*H_3), 30.5 (*C*H_2CH_3), 12.6 (CH*C*H_3), 11.9 (CH_2*C*H_3); MS (APCI, pos.): *m*/*z* 324.1 $(M+1(^{79}Br))^+$ and 326.1 $(M+1(^{81}Br))^+$; HRMS (APPI, pos.): *m*/*z* 323.0507 (323.0521 calc. for $C_{15}H_{18}{}^{79}BrNO_2$ (M^+)) and 326.0560 (325.0579 calc. for $C_{15}H_{18}{}^{81}BrNO_2$ $(M+H)^+$).

(*S*,*Z*)-2-(1-Bromoethylidene)-4,5-dimethyl-6,6-diphenylmorpholin-3-one (95):



This was prepared according to the general procedure. Reaction of the alkene **91** (1.10 g, 3.58 mmol) in CH_2Cl_2 (15 mL) with bromine in water (4.29 mL of a 1.00 M soln., 4.29 mmol) provided 1.58 g of the crude bromohemiacetal as a white foam. This was dehydrated in acetic anhydride (10 mL) and conc. H_2SO_4 (0.10 mL) to provide, after purification by flash chromatography on silica gel (hexane/EtOAc, 3:1), 1.17 g (85% over two steps) of **95** as a white solid. R_f = 0.32 (hexanes/EtOAc, 7:3); mp: 130.0-131.3 °C; $[\alpha]_D^{20}$ = – 149.6° (c 1, CH_2Cl_2); IR (neat): 1652, 1604, 1448, 1308, 1266, 1203, 1147, 972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H, Ar*H*), 7.42-7.37 (m, 2H, Ar*H*), 7.34-7.27 (m, 4H, Ar*H*), 7.23-7.17 (m, 2H, Ar*H*), 4.38 (q, 1H, *J* = 6.5 Hz, C*H*CH_3), 3.05 (s, 3H, NC*H*$_3$), 2.81 (s, 3H, CC*H*$_3$), 1.10 (d, 3H, *J* = 6.5 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4 (N*C*=O), 141.8 (Ar*C*$_{ipso}$), 141.7 (Ar*C*$_{ipso}$), 138.6 (*C*-C=O), 128.9 (2 × Ar*C*), 128.5 (2 × Ar*C*), 127.9 (Ar*C*), 127.2 (Ar*C*), 125.7 (2 × Ar*C*), 124.9 (2 × Ar*C*), 119.1 (C=*C*Br), 83.4 (*C*Ph$_2$), 58.8 (*C*HCH$_3$), 33.9 (N-*C*H$_3$), 25.0 (H$_3$*C*C=C), 14.6 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 386.1 $(M+1(^{79}Br))^+$ and 388.1 $(M+1(^{81}Br))^+$; HRMS (EI, pos.): *m*/*z* 385.0687 (385.0677 calc. for $C_{20}H_{20}{}^{79}BrNO_2$ (M^+)) and 387.0671 (387.0657 calc. for $C_{20}H_{20}{}^{81}BrNO_2$ (M^+)).

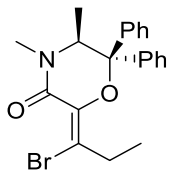
(*S*,*Z*)-2-(1-Bromopropylidene)-4,5-dimethyl-6,6-diphenylmorpholin-3-one (96):



This was prepared according to the general procedure. Reaction of the alkene **92** (457 mg, 1.42 mmol) with bromine in water (1.70 mL of a 1.00 M soln., 1.70 mmol) provided 584 mg (1.40 mmol) of the crude bromohemiacetal as white foam. This was

dehydrated in acetic anhydride (5 mL) and conc. H_2SO_4 (5 drops) for 6 h to provide, after purification by flash chromatography on silica gel (hexanes/EtOAc, 17:3), 426 mg (75% over two steps) of **96** as a reddish brown solid. R_f = 0.46 (EtOAc/hexanes, 3:7); mp = 113.1-115.1 °C; $[\alpha]_D^{25}$ = – 138.0 (c 1, CH_2Cl_2); IR (neat): 2961, 2931, 1663, 1648, 1615, 1599, 1474, 1447, 1397, 1316, 1269, 1206, 1153, 994, 980 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53-7.47 (m, 2H, Ar*H*), 7.42-7.36 (m, 2H, Ar*H*), 7.35-7.26 (m, 4H, Ar*H*), 7.23-7.16 (m, 2H, Ar*H*), 4.37 (q, 1H, *J* = 6.5 Hz, C*H*CH_3), 3.15 (ABX_3, 2H, J_{AB} = 15.1 Hz, J_{AX} = J_{BX} = 7.2 Hz, C=CC$H_2$$CH_3$), 3.04 (s, 3H, NC$H_3$), 1.11 (t, 3H, *J* = 7.2 Hz, C=CCH_2CH_3), 1.11 (d, 3H, *J* = 6.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3 (N*C*=O), 142.0 (ArC_{ipso}), 141.8 (ArC_{ipso}), 138.3 (*C*-C=O), 129.0 (2 × Ar*C*), 128.7 (2 × Ar*C*), 128.0 (Ar*C*), 127.5 (C=*C*Br), 127.4 (Ar*C*), 125.9 (2 × Ar*C*), 125.1 (2 × Ar*C*), 83.7 (*C*Ph_2), 59.0 (*C*HCH_3), 34.1 (N*C*H_3), 30.6 (C=C*C*$H_2$$CH_3$), 14.8 (C=C$CH_2$*C*$H_3$), 14.0 (CH*C*$H_3$); MS (APCI, pos.): *m/z* 400.1 (M+1(^{79}Br))$^+$ and 402.1 (M+1(^{81}Br))$^+$; HRMS (APPI, pos.): *m/z* 399.0837 (399.0834 calc. for $C_{21}H_{22}{}^{79}BrNO_2$ (M^+)) and 402.0891 (402.0891 calc. for $C_{21}H_{23}{}^{81}BrNO_2$ $(M+H)^+$).

(*S*,*E*)-2-(1-Bromopropylidene)-4,5-dimethyl-6,6-diphenylmorpholin-3-one (*E*-96):



Dehydration of the bromohemiacetal obtained from **92** (60 mg, 0.14 mmol) at 50 °C provided a mixture of **96** and ***E*-96** which was separated by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 98:2) to provide and 41 mg (72%) of **96** and 4 mg (7%) of ***E*-96** as a yellow solid. R_f =0.24 (CH_2Cl_2/EtOAc, 97:3); mp = 119.8-121.8 °C; $[\alpha]_D^{25}$ = – 48.0 (c 0.3, CH_2Cl_2); IR (neat): 2964, 2922, 2852, 1649, 1600, 1449, 1400, 1310, 1257, 1199, 1181,

1148, 1102, 1000, 981 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.27 (m, 8H, Ar*H*), 7.25-7.18 (m, 2H, Ar*H*), 4.34 (q, 1H, *J* = 6.5 Hz, C*H*CH_3), 3.08 (s, 3H, NC*H*$_3$), 2.97 (ABX_3, 2H, J_{AB} = 13.9 Hz, J_{AX} = J_{BX} = 7.3 Hz, C=CC*H*$_2$$CH_3$), 1.27 (t, 3H, *J* = 7.4 Hz, C=CCH_2C*H*$_3$), 1.09 (d, 3H, *J* = 6.5 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 (N*C*=O), 142.0 (ArC_{ipso}), 141.6 (ArC_{ipso}), 138.0 (*C*-C=O), 128.9 (2 × Ar*C*), 128.5 (2 × Ar*C*), 128.0 (Ar*C*), 127.3 (Ar*C*), 126.1 (2 × Ar*C*), 124.8 (2 × Ar*C*), 118.5 (C=*C*Br), 82.7 (*C*Ph_2), 58.8 (*C*HCH_3), 34.3 (N*C*H_3), 30.4 (C=C*C*$H_2$$CH_3$), 14.7 (C=C$CH_2$*C*$H_3$), 12.7 (CH*C*$H_3$); MS (APCI, pos.): *m/z* 400.1 $(M+1(^{79}Br))^+$ and 402.1 $(M+1(^{81}Br))^+$; HRMS (APPI, pos.): *m/z* 399.0832 (399.0834 calc. for $C_{21}H_{22}{}^{79}BrNO_2$ (M^+)) and 402.0887 (402.0891 calc. for $C_{21}H_{23}{}^{81}BrNO_2$ $(M+H)^+$).

General Procedure 1 for Suzuki coupling with arylboronic acids:

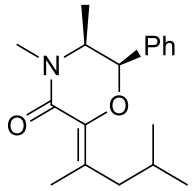
To the bromoalkene at room temperature were added the arylboronic acid, Cs_2CO_3 and CH_3CN (purged with N_2 for 15 min) followed by $PdCl_2(dppf)\cdot CH_2Cl_2$. The mixture was heated to reflux until complete consumption of the bromoalkene (TLC), then cooled to room temperature and aqueous saturated NH_4Cl (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined extracts were washed with aq. NaOH (10%), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

General Procedure 2 for Suzuki coupling with alkyltrifluoroborates:

To the bromoalkene at room temperature were added the alkyl trifluoroborate salt, Cs_2CO_3, a mixture of toluene and water (3:1, purged with N_2 for 15 min) followed by

$PdCl_2(dppf)\cdot CH_2Cl_2$. The mixture was heated at 80 °C until complete consumption of the bromoalkene (TLC), then cooled to room temperature and aqueous saturated NH_4Cl (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

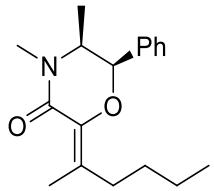
(5*S*,6*R*,*Z*)-2-(4-Methylpentan-2-ylidene)-4,5-dimethyl--6-phenylmorpholin-3-one (97):



The reaction of bromoalkene **86** (58 mg, 0.18 mmol), potassium 2-methylpropyltrifluoroborate (0.24 mmol), Cs_2CO_3 (0.56 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.018 mmol) in toluene/water (3:1, 2 mL) for 24 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 9:1), 43 mg (80%) of **97** as a colorless liquid. R_f = 0.27 (hexane/EtOAc, 7:3); $[\alpha]_D^{20}$ = –107.2 (c 1, CH_2Cl_2); IR (neat): 2957, 1661, 1451, 1399, 1379, 1294, 1266, 1161, 1143, 1068, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H, Ar*H*), 5.10 (d, 1H, *J* = 2.6 Hz, C*H*Ph), 3.53 (dq, 1H, *J* = 6.5, 2.6 Hz, C*H*CH_3), 3.06 (s, 3H, NCH_3), 2.23 (s, 3H, C=CCH_3), 2.21 (ABX, 2H, J_{AB} = 12.2 Hz, J_{AX} = 7.5 Hz, J_{BX} = 6.8 Hz, C=CCH_2), 1.96-1.80 (septet, 1H, *J* = 6.8 Hz, CH_3CHCH_3), 0.96 (d, 3H, *J* = 2.4 Hz, CH_3CHCH_3), 0.93 (d, 3H, *J* = 2.4 Hz, CH_3CHCH_3), 0.89 (d, 3H, *J* = 6.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1 (N*C*=O), 138.8 (ArC_{ipso} or *C*-*C*=O), 137.7 (ArC_{ipso} or *C*-*C*=O), 130.5 (C=*C*CH_3), 128.4 (2

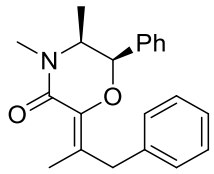
× Ar*C*), 127.7 (Ar*C*), 125.4 (2 × Ar*C*), 76.8 (Ph*C*), 58.9 (*C*HCH$_3$), 42.9 (C=C*C*H$_2$), 33.5 (N*C*H$_3$), 27.1 (CH$_3$*C*HCH$_3$), 22.7 (CH$_3$CH*C*H$_3$), 18.9 (H$_3$*C*C=C), 12.0 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 288.2 (M+H)$^+$; HRMS (EI, pos.): *m*/*z* 287.1887 (287.1885 calc. for $C_{18}H_{25}NO_2$ (M^+)).

(5*S*,6*R*,*Z*)-2-(Hexan-2-ylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (103):



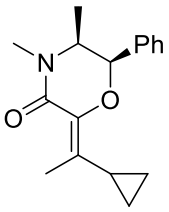
The reaction of bromoalkene **86** (300 mg, 0.970 mmol), potassium *n*-butyltrifluoroborate (3.88 mmol), Cs_2CO_3 (2.91 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (0.097 mmol) in toluene/water (3:1, 5 mL) for 3 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 97:3), 257 mg (92%) of **103** as a pale-yellow liquid. R_f = 0.26 (CH_2Cl_2/EtOAc, 96:4); $[\alpha]_D^{20}$ = – 118.4 (c 0.74, CH_2Cl_2); IR (neat): 1659, 1617, 1443, 1386, 1286, 1211, 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 5H, Ar*H*), 5.12 (d, 1H, *J* = 2.7 Hz, PhC*H*), 3.54 (dq, 1H, *J* = 6.6, 2.7 Hz, NC*H*), 3.06 (s, 3H, NC*H*$_3$), 2.39-2.24 (m, 2H, C=CC*H*$_2$), 2.24 (s, 3H, C=CC*H*$_3$), 1.52-1.40 (m, 2H, C*H*$_2$CH$_2$), 1.38-1.28 (m, 2H, CH$_2$C*H*$_2$), 0.95 (d, 3H, *J* = 6.6 Hz, CHC*H*$_3$), 0.90 (t, 3H,*J* = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (*C*=O), 138.4 (*C*-C=O), 137.7 (ArC_{ipso}), 131.2 (C=*C*CH$_2$CH$_3$), 128.4 (2 x Ar*C*), 127.7(Ar*C*), 125.4 (2 x Ar*C*), 76.8 (Ph*C*H), 58.9 (N*C*H), 33.44 (N*C*H$_3$), 33.42 (C=C*C*H$_2$), 29.6 (*C*H$_2$), 22.6 (*C*H$_2$), 18.4 (C=C*C*H$_3$), 14.0 (CH$_2$*C*H$_3$), 11.9 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 288.3 (M+H)$^+$; HRMS (EI, pos.): *m*/*z* 287.1887 (287.1885 calc. for $C_{18}H_{25}NO_2$ (M^+)).

(5*S*,6*R*,*Z*)-4,5-Dimethyl-6-phenyl-2-(1-phenylpropan-2-ylidene)morpholin-3-one (104):



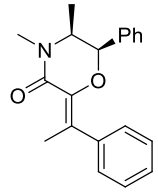
The reaction of bromoalkene **86** (51 mg, 0.16 mmol), benzylboronic acid pinacol ester (0.33 mmol), Cs_2CO_3 (0.33 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.016 mmol) in CH_3CN (2 mL) for 1 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2), 38 mg (72%) of **104** as a colorless liquid. R_f = 0.43 (CH_2Cl_2/EtOAc, 96:4); $[\alpha]_D^{20}$ = – 54.7 (c 0.75, CH_2Cl_2); IR (neat): 2980, 2925, 1655, 1624, 1451, 1398, 1378, 1290, 1159, 1087, 1067, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.14 (m, 10H, Ar*H*), 5.20 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 3.78 (d, 1H, *J* = 13.7 Hz, CH_2Ph), 3.57 (dq, 1H, *J* = 6.5, 2.7 Hz, C*H*CH_3), 3.54 (d, 1H, *J* = 13.5 Hz, CH_2Ph), 3.08 (s, 3H, NCH_3), 2.20 (s, 3H, C=CCH_3), 1.00 (d, 3H, *J* = 6.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9 (N*C*=O), 139.8 (ArC_{ipso} or *C*-C=O), 138.8 (ArC_{ipso} or *C*-*C*=O), 137.4 (ArC_{ipso} or *C*-*C*=O), 129.1 (C=*C*CH_3), 128.9 (2 × Ar*C*), 128.5 (2 × Ar*C*), 128.4 (2 × Ar*C*), 127.8 (Ar*C*), 126.0 (Ar*C*), 125.5 (2 × Ar*C*), 77.2 (Ph*C*), 59.0 (*C*HCH_3), 39.3 (CH_2Ph), 33.6 (N*C*H_3), 18.2 (H_3*C*C=C), 12.1 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 322.2 $(M+H)^+$; HRMS (EI, pos.): *m*/*z* 321.1740 (321.1729 calc. for $C_{21}H_{23}NO_2$ (M^+)).

(5*S*,6*R*,*Z*)-2-(1-Cyclopropylethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (105):



The reaction of bromoalkene **86** (140 mg, 0.450 mmol), potassium cyclopropyltrifluoroborate (1.80 mmol), Cs_2CO_3 (1.80 mmol) and $PdCl_2(dppf)•CH_2Cl_2$ (0.045 mmol) in toluene/water (3:1, 2 mL) for 66 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 98:2), 88 mg (72%, 75% based on recovery of **86**) of **105** as a white solid. R_f = 0.33 (CH_2Cl_2/EtOAc, 96:4); mp = 118.0-120.1 °C; $[\alpha]_D^{20}$ = – 169.6 (c 1.1, CH_2Cl_2); IR (neat): 2970, 2928, 2863, 1644, 1605, 1439, 1395, 1376, 1298, 1252, 1212, 1164, 1066, 1027, 918, 895 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.43-7.35 (m, 4H, Ar*H*), 7.35-7.28 (m, 1H, Ar*H*), 5.17 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 3.55 (dq, 1H, *J* = 6.5, 2.7 Hz, C*H*CH_3), 3.06 (s, 3H, NC*H*$_3$), 2.40-2.32 (m, 1H, C=CC*H*), 1.85 (s, 3H, C=CC*H*$_3$), 0.98 (d, 3H, *J* = 6.5 Hz, C*H*$_3$CH), 0.82-0.75 (m, 1H, C*H*$_2$CH$_2$), 0.70-0.63 (m, 3H, C*H*$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (N*C*=O), 139.2 (ArC_{ipso} or *C*-*C*=O), 137.7 (ArC_{ipso} or *C*-*C*=O), 131.2 (C=*C*CH_3), 128.4 (2 × Ar*C*), 127.7 (Ar*C*), 125.5 (2 × Ar*C*), 77.1 (Ph*C*), 58.8 (*C*HCH_3), 33.5 (N-*C*H$_3$), 12.3 (CH*C*H$_3$), 12.0 (H*C*C=C), 11.1 (H$_3$*C*C=C), 5.0 (*C*H$_2$CH$_2$), 4.9 (CH$_2$*C*H$_2$); MS (APCI, pos.): *m*/*z* 272.1 $(M+H)^+$. HRMS (EI, pos.): *m*/*z* 271.1581 (271.1572 calc. for $C_{17}H_{21}NO_2$ (M^+)).

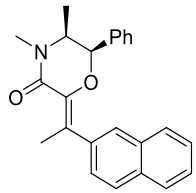
(5*S*,6*R*,*Z*)-4,5-Dimethyl-6-phenyl-2-(1-phenylethylidene)morpholin-3-one (106):



The reaction of bromoalkene **86** (300 mg, 0.970 mmol), phenylboronic acid (1.94 mmol), Cs_2CO_3 (1.94 mmol) and $PdCl_2(dppf)·CH_2Cl_2$ (0.097 mmol) in CH_3CN (5 mL) for

2 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 98:2), 274 mg (92%) of **107** as a light brown gum. R_f = 0.31 (CH_2Cl_2/EtOAc, 96:4); $[\alpha]_D^{20}$ = –170.8 (c 1.1, CH_2Cl_2); IR (neat): 1649, 1606, 1490, 1440, 1295, 1256, 1176, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.19 (m, 8H, Ar*H*), 7.14-7.09 (m, 2H, Ar*H*), 5.18 (d, 1H, *J* = 2.7 Hz, PhC*H*), 3.60 (dq, 1H, *J* = 6.5, 2.7 Hz, NC*H*), 3.12 (s, 3H, NCH_3), 2.57 (s, 3H, C=CCH_3), 0.96 (d, 3H, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (*C*=O), 141.7 (*C*-C=O), 138.7 (ArC_{ipso}), 137.0 (C=*C*CH_3), 128.4 (2 x Ar*C*), 128.3 (2 x Ar*C*), 128.1 (Ar*C*), 127.7 (2 x Ar*C*), 127.6 (Ar*C*), 126.9 (Ar*C*), 125.3 (2 x Ar*C*), 77.03 (Ph*C*H), 58.8 (N*C*H), 33.7 (N*C*H_3), 20.1 (C=C*C*H_3), 12.0 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 308.4 $(M+H)^+$; HRMS (EI): *m*/*z* 307.1574 (307.1572 calc. for $C_{20}H_{21}NO_2$ (M^+)).

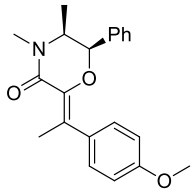
(5*S*,6*R*,*Z*)-4,5-Dimethyl-2-(1-(naphthalen-2-yl)ethylidene)-6-phenylmorpholin-3-one (107):



The reaction of bromoalkene **86** (68 mg, 0.22 mmol), 2-naphthylboronic acid (0.44 mmol), Cs_2CO_3 (0.44 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.022 mmol) in CH_3CN (2 mL) for 3 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1), 75 mg (96%) of **107** as a light yellow solid. R_f = 0.31 (CH_2Cl_2/EtOAc, 97:3); mp = 112.9-114.3 °C; $[\alpha]_D^{20}$ = – 159.6 (c 1, CH_2Cl_2); IR (neat): 2977, 2930, 2908, 2856, 1650, 1615, 1439, 1378, 1287, 1259, 1210, 1173, 1149, 1025, 821

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (br s, 1H, Ar*H*), 7.84-7.72 (m, 3H, Ar*H*), 7.54 (dd, 1H, *J* = 8.5, 1.1 Hz, Ar*H*), 7.47-7.40 (m, 2H, Ar*H*), 7.26-7.08 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.6 Hz, C*H*Ph), 3.60 (dq, 1H, *J* = 6.6, 2.6 Hz, C*H*CH_3), 3.13 (s, 3H, NC*H*$_3$), 2.68 (s, 3H, C=CC*H*$_3$), 0.97 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (N*C*=O), 139.3 (Ar*C*$_{ipso}$ or *C*-*C*=O), 139.2 (Ar*C*$_{ipso}$ or *C*-*C*=O), 137.0 (Ar*C*$_{ipso}$), 133.2 (Ar*C*), 132.5 (Ar*C*), 128.4 (2 × Ar*C*), 128.1 (Ar*C*), 127.9 (C=*C*CH_3), 127.6 (2 × Ar*C*), 127.3 (Ar*C*), 127.2 (Ar*C*), 126.9 (Ar*C*), 125.94 (Ar*C*), 125.88 (Ar*C*), 125.3 (Ar*C*), 77.2 (Ph*C*), 58.8 (*C*HCH_3), 33.8 (N*C*H_3), 20.3 (H_3*C*C=C), 12.0 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 358.2 $(M+H)^+$; HRMS (APPI, pos.): *m*/*z* 357.1734 (357.1729 calc. for $C_{24}H_{23}NO_2$ (M^+)).

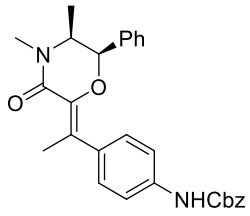
(5*S*,6*R*,*Z*)-2-(1-(4-Methoxyphenyl)ethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (108):



The reaction of bromoalkene **86** (360 mg, 1.16 mmol), 4-methoxyphenylboronic acid (2.32 mmol), Cs_2CO_3 (2.32 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.116 mmol) in CH_3CN (5 mL) for 3 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 97:3), 371 mg (94%) of **108** as a brown solid. R_f = 0.30 (CH_2Cl_2/EtOAc, 96:4); mp = 125.3-126.7 °C; $[\alpha]_D^{20}$ = – 220.8 (c 1, CH_2Cl_2); IR (neat): 1654, 1606, 1508, 1438, 1386, 1289, 1246, 1175, 1107, 1026, 830, 758, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-34 (m, 2H, Ar*H*), 7.33-7.23 (m, 3H, Ar*H*), 7.21-7.15 (m, 2H, Ar*H*), 6.90-6.83 (m, 2H, Ar*H*), 5.18 (d, 1H, *J* = 2.7 Hz, PhC*H*), 3.81 (s,

3H, OC*H*$_3$), 3.60 (dq, 1H, *J* = 6.5, 2.7 Hz, NC*H*), 3.11 (s, 3H, NC*H*$_3$), 2.56 (s, 3H, C=CC*H*$_3$), 0.96 (d, 3H, *J* = 6.5 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3 (*C*=O), 158.4 (Ar*C*$_{ipso}$), 138.5 (Ar*C*$_{ipso}$), 137.0 (Ar*C*$_{ipso}$), 133.8 (*C*-C=O), 129.8 (2 x Ar*C*), 128.3 (2 x Ar*C*), 127.7 (C=*C*CH$_3$), 127.5 (Ar*C*), 125.3 (2 x Ar*C*), 113.0 (2 x Ar*C*), 77.1 (Ph*C*H), 58.8 (N*C*H), 55.2 (O*C*H$_3$), 33.7 (N*C*H$_3$), 20.1 (C*C*H$_3$), 11.9 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 338.3 $(M+H)^+$; HRMS (EI pos.): *m*/*z* 337.1677 (337.1678 calc. for $C_{21}H_{23}NO_3$ (M^+)).

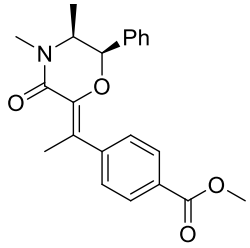
Benzyl-4-((*Z*)-1-((5*S*,6*R*)-4,5-dimethyl-3-oxo-6-phenylmorpholin-2-ylidene)ethyl)phenylcarbamate (109):



The reaction of bromoalkene **86** (180 mg, 0.580 mmol), 4-Cbz-aminophenyl boronic acid (1.16 mmol), Cs_2CO_3 (1.16 mmol) and $PdCl_2$(dppf)•CH_2Cl_2 (0.058 mmol) in CH_3CN (4 mL) for 2.5 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 94:6), 234 mg (88%) of **109** as a light brown solid. R_f = 0.32 (CH_2Cl_2/EtOAc, 9:1); mp = 160.6-162.1 °C; $[\alpha]_D^{20}$ = – 170 (c 0.5, CH_2Cl_2); IR (neat): 3285, 2977, 2934, 2898, 1718, 1602, 1518, 1442, 1394, 1376, 1318, 1255, 1210, 1174, 1135, 1048, 1026, 1006, 978 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.20 (m, 12 H, Ar*H*), 7.19-7.13 (m, 2H, Ar*H*) 6.71 (br s, 1H, N*H*CO), 5.21 (s, 2H, PhC*H*$_2$), 5.17 (d, 1H, *J* = 2.7 Hz, PhC*H*), 3.58 (dq, 1H, *J* = 6.5, 2.7 Hz, C*H*CH$_3$), 3.11 (s, 3H, NC*H*$_3$), 2.55 (s, 3H, C=CC*H*$_3$), 0.96 (d, 3H, *J* = 6.5 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3 (N*C*=O), 153.4 (ArNH*C*O), 138.9 (Ar*C*$_{ipso}$ or *C*-*C*=O), 137.1 (Ar*C*$_{ipso}$ or *C*-*C*=O),

136.8 (Ar*C*$_{ipso}$ or *C*-*C*=O), 136.6 (Ar*C*$_{ipso}$ or *C*-*C*=O), 136.2 (Ar*C*$_{ipso}$ or *C*-*C*=O), 129.5 (2 × Ar*C*), 128.7 (2 × Ar*C*), 128.51 (2 × Ar*C*), 128.47 (2 × Ar*C*), 128.4 (2 × Ar*C*), 127.7 (Ar*C*), 127.4 (C=*C*CH$_3$), 125.4 (2 × Ar*C*), 117.9 (Ar*C*), 77.3 (Ph*C*H), 67.1 (Ph*C*H$_2$O), 58.9 (*C*HCH$_3$), 33.9 (N*C*H$_3$), 20.1 (C=C*C*H$_3$), 12.1 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 457.2 $(M+H)^+$; HRMS (APPI, pos.): *m*/*z* 456.2063 (456.2049 calc. for $C_{28}H_{28}N_2O_4$ (M^+)).

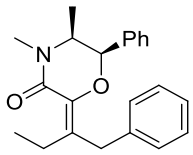
Methyl-4-((*Z*)-1-((5*S*,6*R*)-4,5-dimethyl-3-oxo-6-phenylmorpholin-2-ylidene)ethyl)benzoate (110):



The reaction of bromoalkene **86** (230 mg, 0.740 mmol), 4-methoxycarbonylphenylboronic acid (1.48 mmol), Cs_2CO_3 (1.48 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (0.074 mmol) in CH_3CN (4 mL) for 3 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 92:8), 241 mg (89%) of **110** as a light brown solid. R_f = 0.25 (CH_2Cl_2/EtOAc, 9:1); mp = 136.1-137.9 °C; $[\alpha]_D^{20}$ = – 220.4 (c 1, CH_2Cl_2); IR (neat): 1706, 1610, 1472, 1440, 1392, 1273, 1179, 1104, 1021, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 2H, *J* = 8.5 Hz, Ar*H*), 7.45 (d, 2H, *J* = 8.5 Hz, Ar*H*), 7.33-7.23 (m, 3H, Ar*H*), 7.13-7.08 (m, 2H, Ar*H*), 5.20 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 3.92 (s, 3H, OC*H*$_3$), 3.60 (dq, 1H, *J* = 6.5, 2.7 Hz, C*H*CH$_3$), 3.13 (s, 3H, NC*H*$_3$), 2.56 (s, 3H, C=CC*H*$_3$), 0.97 (d, 3H, *J* = 6.5 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (*C*O$_2$CH$_3$), 160.8 (N*C*=O), 146.7 (Ar*C*$_{ipso}$), 139.3 (Ar*C*$_{ipso}$ or *C*-*C*=O), 136.8 (Ar*C*$_{ipso}$ or *C*-*C*=O), 129.1 (2 × Ar*C*), 128.6 (2

× Ar*C*), 128.55 (2 × Ar*C*), 128.49 (ArC_{ipso} or *C*-*C*=O), 127.8 (Ar*C*), 126.8 (C=*C*CH_3), 125.7 (2 × Ar*C*), 77.3 (Ph*C*), 58.9 (*C*HCH_3), 52.2 (OCH_3), 33.8 (NCH_3), 19.9 (H_3*C*C=C), 12.0 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 366.2 $(M+H)^+$; HRMS (APPI, pos.): *m*/*z* 365.1635 (365.1627 calc. for $C_{22}H_{23}NO_4$ (M^+)).

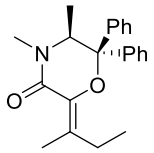
(5*S*,6*R*,*Z*)-4,5-Dimethyl-6-phenyl-2-(1-phenylbutan-2-ylidene)morpholin-3-one (111):



The reaction of bromoalkene **87** (85 mg, 0.26 mmol), potassium benzyltrifluoroborate (0.79 mmol), Cs_2CO_3 (0.79 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (0.026 mmol) in toluene/water (3:1, 2 mL) for 2 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 98:2), 75 mg (85%) of **111** as a colorless liquid. R_f = 0.32 (CH_2Cl_2/EtOAc, 97:3); $[\alpha]_D^{20}$ = –20.6 (c 1.6, CH_2Cl_2); IR (neat): 2975, 2930, 2871, 1654, 1620, 1450, 1395, 1285, 1209, 1159, 1049, 1012 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.13 (m, 10H, Ar*H*), 5.18 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 3.83 (d, 1H, *J* = 13.8 Hz, CH_2Ph), 3.55 (dq, 1H, *J* = 6.5, 2.7 Hz, C*H*CH_3), 3.51 (d, 1H, *J* = 13.8 Hz, CH_2Ph), 3.08 (s, 3H, NCH_3), 2.80 (ABX_3, 1H, J_{AB} = 12.5 Hz, J_{AX} = J_{BX} = 7.4 Hz, C$H_2$$CH_3$), 2.48 ($ABX_3$, 1H, J_{AB} = 12.5 Hz, J_{AX} = J_{BX} = 7.4 Hz, C$H_2$$CH_3$), 1.08 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 0.99 (d, 3H, *J* = 6.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3 (N*C*=O), 140.1 (ArC_{ipso} or *C*-C=O), 138.8 (ArC_{ipso} or *C*-*C*=O), 137.3 (ArC_{ipso} or *C*-*C*=O), 134.8 (C=*C*CH_2), 128.8 (2 × Ar*C*), 128.4 (2 × Ar*C*), 128.3 (2 × Ar*C*), 127.8 (Ar*C*), 125.9 (Ar*C*), 125.5 (2 × Ar*C*), 77.1 (Ph*C*H), 58.8 (*C*HCH_3), 36.7 (*C*H_2Ph),

33.5 (N*C*H$_3$), 24.3 (H$_2$*C*C=C), 13.4 (CH*C*H$_3$), 12.0 (CH$_2$*C*H$_3$); MS (APCI, pos.): *m*/*z* 336.2 (M+H)$^+$; HRMS (EI, pos.): *m*/*z* 335.1883 (335.1885 calc. for $C_{22}H_{25}NO_2$ (M^+)).

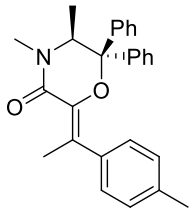
(*S*,*Z*)-2-(Butan-2-ylidene)-4,5-dimethyl-6,6-diphenylmorpholin-3-one (112):



The reaction of bromoalkene **95** (60 mg, 0.15 mmol), potassium ethyltrifluoroborate (0.62 mmol), Cs_2CO_3 (0.46 mmol) and $PdCl_2$(dppf)•CH_2Cl_2 (0.015 mmol) in toluene/water (3:1, 2 mL) for 19 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1), 42 mg (80%, 87% based on recovery of **95**) of **112** as a white solid. R_f = 0.30 (CH_2Cl_2/EtOAc, 98:2); mp = 160.4-162.5 °C; $[\alpha]_D^{20}$ = –225.8 (c 0.82, CH_2Cl_2); IR (neat): 2962, 2932, 1648, 1613, 1475, 1450, 1399, 1375, 1313, 1259, 1159, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.36 (m, 2H, Ar*H*), 7.34-7.15 (m, 8H, Ar*H*), 4.30 (q, 1H, *J* = 6.4 Hz, C*H*CH$_3$), 3.05 (s, 3H, NC*H*$_3$), 2.60 (ABX$_3$, 1H, J_{AB} = 12.7 Hz, J_{AX} = J_{BX} = 7.4 Hz, C*H*$_2$CH$_3$), 2.38 (ABX$_3$, 1H, J_{AB} = 12.7 Hz, J_{AX} = J_{BX} = 7.4 Hz, C*H*$_2$CH$_3$), 2.14 (s, 3H, C=CC*H*$_3$), 1.18 (t, 3H, *J* = 7.5 Hz, CH$_2$C*H*$_3$), 1.06 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8 (N*C*=O), 142.9 (Ar*C*$_{ipso}$), 142.5 (Ar*C*$_{ipso}$), 135.8 (*C*-C=O), 132. 5 (H$_3$C*C*=C), 128.6 (2 × Ar*C*), 128.4 (2 × Ar*C*), 127.5 (Ar*C*), 127.0 (Ar*C*), 126.2 (2 × Ar*C*), 125.0 (2 × Ar*C*), 81.5 (*C*Ph$_2$), 58.7 (*C*HCH$_3$), 33.9 (N*C*H$_3$), 27.0 (CH$_3$H$_2$*C*C=C), 17.8 (*C*H$_3$C=C), 14.7 (CH*C*H$_3$), 11.9 (*C*H$_3$H$_2$CC=C); MS (APCI, pos.): *m*/*z* 336.2 (M+H)$^+$; HRMS (EI, pos.): *m*/*z* 335.1887 (335.1885 calc. for $C_{22}H_{25}NO_2$ (M^+)).

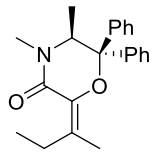
A similar reaction of bromoalkene ***E*-96** and potassium methyltrifluoroborate provided **112** (50%) as a white solid.

(*S*,*Z*)-4,5-Dimethyl-6,6-diphenyl-2-(1-p-tolylethylidene)morpholin-3-one (113):



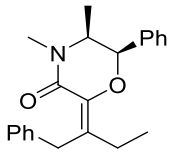
The reaction of bromoalkene **95** (150 mg, 0.380 mmol), 4-methylphenylboronic acid (0.77 mmol), Cs_2CO_3 (0.77 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.038 mmol) in CH_3CN (4 mL) for 2.5 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1), 144 mg (93%) of **113** as a white solid. R_f = 0.30 (CH_2Cl_2/EtOAc, 98:2); mp = 163.1-164.5 °C; $[\alpha]_D^{20}$ = –170.4 (c 1, CH_2Cl_2); IR (neat): 3024, 2981, 1639, 1607, 1475, 1450, 1398, 1320, 1265, 1173, 1152, 1126, 976, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.34 (m, 2H, Ar*H*), 7.29-7.06 (m, 12H, Ar*H*), 4.33 (q, 1H, *J* = 6.4 Hz, C*H*CH_3), 3.09 (s, 3H, NC*H*$_3$), 2.43 (s, 3H, C=CC*H*$_3$), 2.42 (s, 3H, ArC*H*$_3$), 1.12 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (N*C*=O), 142.5 (Ar*C*$_{ipso}$), 142.0 (Ar*C*$_{ipso}$), 139.3 (*C*-*C*=O), 136.5 (2 × Ar*C*$_{ipso}$), 129.7 (H_3C*C*=C), 128.5 (4 × Ar*C*), 128.2 (4 × Ar*C*), 127.5 (Ar*C*), 126.8 (Ar*C*), 126.2 (2 × Ar*C*), 125.0 (2 × Ar*C*), 82.5 (Ph_2*C*), 58.6 (*C*HCH_3), 34.0 (N*C*H$_3$), 21.3 (C=C*C*H$_3$), 20.4 (Ar*C*H$_3$) 14.7 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 398.3 $(M+H)^+$; HRMS (APPI, pos.): *m*/*z* 397.2047 (397.2042 calc. for $C_{27}H_{27}NO_2$ (M^+)), 398.2120 (398.2118 calc. for $C_{27}H_{28}NO_2$ $(M+H)^+$).

(*S*,*E*)-2-(Butan-2-ylidene)-4,5-dimethyl-6,6-diphenylmorpholin-3-one (114):



The reaction of bromoalkene **96** (50 mg, 0.12 mmol), potassium methyltrifluoroborate (0.37 mmol), Cs_2CO_3 (0.37 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.012 mmol) in toluene and water (3:1, 2 mL) for 37 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (CH_2Cl_2), 23 mg (55%, 64% based on recovery of **96**) of **114** as a white solid. R_f = 0.30 (CH_2Cl_2/EtOAc, 98:2); mp = 119.5-121.3 °C; $[\alpha]_D^{20}$ = –220.6 (c 1, CH_2Cl_2); IR (neat): 2964, 2936, 1644, 1611, 1450, 1399, 1313, 1277, 1159, 1137, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.38 (m, 2H, Ar*H*), 7.35-7.14 (m, 8H, Ar*H*), 4.30 (q, 1H, *J* = 6.4 Hz, C*H*CH_3), 3.04 (s, 3H, NC*H*$_3$), 2.72 (ABX_3, 1H, J_{AB} = 12.7 Hz, J_{AX} = J_{BX} = 7.4 Hz, C*H*$_2$$CH_3$), 2.56 ($ABX_3$, 1H, J_{AB} = 12.7 Hz, J_{AX} = J_{BX} = 7.4 Hz, C*H*$_2$$CH_3$), 2.02 (s, 3H, C=CC*H*$_3$), 1.08 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH), 0.95 (t, 3H, *J* = 7.4 Hz, CH_2C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2 (N*C*=O), 142.9 (ArC_{ipso}), 142.4 (ArC_{ipso}), 136.1 (*C*-C=O), 133.6 (H_3C*C*=C), 128.6 (2 × Ar*C*), 128.3 (2 × Ar*C*), 127.5 (Ar*C*), 127.0 (Ar*C*), 126.0 (2 × Ar*C*), 125.0 (2 × Ar*C*), 81.6 (*C*Ph_2), 58.7 (*C*HCH$_3$), 33.8 (NCH_3), 26.5 (CH_3H_2*C*C=C), 18.0 (*C*H$_3$C=C), 14.7 (CH*C*H$_3$), 13.1 (*C*H_3H_2CC=C); MS (APCI, pos.): *m*/*z* 336.2 $(M+H)^+$; HRMS (APPI, pos.): *m*/*z* 335.1892 (335.1885 calc. for $C_{22}H_{25}NO_2$ (M^+)).

(5*S*,6*R*,*E*)-4,5-Dimethyl-6-phenyl-2-(1-phenylbutan-2-ylidene)morpholin-3-one (*E*-111):



The reaction of bromoalkene ***E*-87** (40 mg, 0.12 mmol), potassiumbenzyltrifluoroborate (0.37 mmol), Cs_2CO_3 (0.37 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.012 mmol) in toluene and water (3:1, 1 mL) for 2 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1), 28 mg (67%) of ***E*-111** as a brown solid. R_f = 0.39 (CH_2Cl_2/EtOAc, 98:2); mp = 98.8-100.5 °C; $[\alpha]_D^{20}$ = –84.4 (c 1.1, CH_2Cl_2); IR (neat): 2971, 2933, 2909, 2849, 1646, 1582, 1462, 1449, 1434, 1394, 1373, 1282, 1234, 1152, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.12 (m, 10H, Ar*H*), 5.20 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 4.69 (d, 1H, *J* = 13.9 Hz, CH_2Ph), 3.99 (d, 1H, *J* = 13.9 Hz, CH_2Ph), 3.58 (dq, 1H, *J* = 6.5, 2.7 Hz, C*H*CH_3), 3.10 (s, 3H, NCH_3), 2.23 (ABX_3, 2H, J_{AB} = 12.6 Hz, J_{AX} = J_{BX} = 7.5 Hz, C$H_2$$CH_3$), 1.00 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 1.00 (d, 3H, *J* = 6.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6 (N*C*=O), 140.5 (ArC_{ipso} or *C*-C=O), 139.4 (ArC_{ipso} or *C*-*C*=O), 137.5 (ArC_{ipso} or *C*-*C*=O), 134.2 (C=*C*CH_2), 129.0 (2 × Ar*C*), 128.5 (2 × Ar*C*), 128.1 (2 × Ar*C*), 127.8 (Ar*C*), 125.7 (Ar*C*), 125.4 (2 × Ar*C*), 77.0 (Ph*C*H), 58.9 (*C*HCH_3), 36.2 (*C*H_2Ph), 33.6 (NCH_3), 24.3 (H_2*C*C=C), 12.2 (CH*C*H_3), 11.9 (CH_2*C*H_3); MS (APCI, pos.): *m*/*z* 336.2 $(M+H)^+$; HRMS (APPI, pos.): *m*/*z* 335.1884 (335.1885 calc. for $C_{22}H_{25}NO_2$ (M^+)).

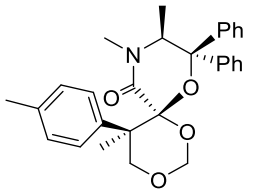
General procedure 3 for the Prins reaction of alkylidene morpholinones:

To a solution of the alkene in TFA was added paraformaldehyde. Depending on the nature of the alkene substituent, the reaction mixture was stirred at ambient temperature (aromatic alkene substituent) or at 0 ^{o}C (aliphatic alkene substituent). After completion of the reaction (TLC), the TFA was removed under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and the solution was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

General procedure 4 for the Prins reaction of alkylidene morpholinones:

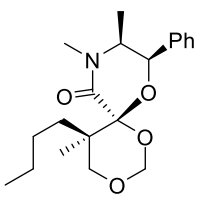
To a mixture of paraformaldehyde in glacial acetic acid was added 2-3 drops of conc. H_2SO_4 and the mixture heated until the paraformaldehyde dissolved (~5 min) in a preheated oil bath set at 85 °C. The mixture was cooled to room temperature, the alkene was added and the reaction mixture was heated at 85 °C. After completion of the reaction (TLC), the mixture was cooled to room temperature and the acetic acid was removed under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and the solution was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

(5*R*,6*R*,9*S*)-5,9,10-Trimethyl-8,8-diphenyl-5-p-tolyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (115):



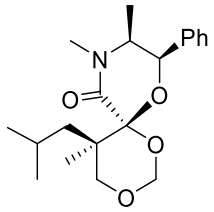
The reaction of alkene **113** (100 mg, 0.250 mmol), paraformaldehyde (1.25 mmol) in TFA (2 mL) for 5.5 days at room temparature according to General Procedure 3 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 3:1), 97 mg (87%) of **115** as a white solid. R_f = 0.30 (hexane/EtOAc, 11:9); mp = 159.2-161.7 °C; $[\alpha]_D^{20}$ = –204.4 (c 1, CH_2Cl_2); IR (neat): 2922, 2880, 1647, 1456, 1323, 1186, 1075, 1028, 994, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.02 (m, 14H, Ar*H*), 5.15 (d, 1H, *J* = 10.5 Hz, OC*H*$_2$), 5.14 (d, 1H, *J* = 5.7 Hz, OC*H*$_2$O), 4.39 (d, 1H, *J* = 5.7 Hz, OC*H*$_2$O), 3.92 (q, 1H, *J* = 6.6 Hz, C*H*CH_3), 3.81 (d, 1H, *J* = 10.5 Hz, OC*H*$_2$), 3.10 (s, 3H, NC*H*$_3$), 2.25 (s, 3H, ArC*H*$_3$), 1.84 (s, 3H, Ar-C-C*H*$_3$), -0.30 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (N*C*=O), 144.2 (Ar*C*$_{ipso}$), 142.8 (Ar*C*$_{ipso}$), 139.3 (Ar*C*$_{ipso}$), 136.7 (Ar*C*$_{ipso}$), 129.0 (3 × Ar*C*), 128.22 (2 × Ar*C*), 128.17 (2 × Ar*C*), 128.1 (Ar*C*), 128.0 (3 × Ar*C*), 127.2 (3 × Ar*C*), 99.2 (O-*C*-O), 86.9 (O*C*H_2O), 80.2 (Ph$_2$*C*), 71.6 (O*C*H_2), 59.8 (*C*HCH_3), 45.5 (Ar-*C*-CH_3), 34.1 (N-*C*H$_3$), 22.6 (Ar*C*H$_3$), 21.0 (Ar-C-*CH*$_3$), 13.3 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 458.3 $(M+H)^+$ and 398.3 $(M-C_2H_4O_2+H)^+$; HRMS (APPI, pos.): *m*/*z* 457.2262 (457.2253 calc. for $C_{29}H_{31}NO_4$ (M^+)) and 397.2047 (397.2042 calc. for $C_{27}H_{27}NO_2$ $(M-C_2H_4O_2)^+$).

(5*R*,6*R*,8*R*,9*S*)-5-Butyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (116):



The reaction of alkene **103** (250 mg, 0.870 mmol), paraformaldehyde (4.35 mmol) in TFA (3 mL) for 23 h at 0 °C according to General Procedure 3 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 7:3), 264 mg (87%) of **116** as a white solid. R_f = 0.27 (hexane/EtOAc, 6:4); mp = 92.3-94.1 °C; $[\alpha]_D^{20}$ = – 46.8 (c 1, CH_2Cl_2); IR (neat): 1656, 1457, 1380, 1288, 1139, 1090, 1024, 976 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.29 (m, 5H, Ar*H*), 5.42 (d, 1H, *J* = 3.0 Hz, PhC*H*), 5.00 (d, 1H, *J* = 5.6 Hz, OC*H*$_2$O), 4.96 (d, 1H, *J* = 5.6 Hz, OC*H*$_2$O), 4.03 (d, 1H, *J* = 10.8 Hz, OC*H*$_2$), 3.71 (d, 1H, *J* = 10.8 Hz, OC*H*$_2$), 3.50 (dq, 1H, *J* = 3.0, 6.5 Hz, NC*H*), 3.01 (s, 3H, NC*H*$_3$), 1.51-1.48 (m, 2H, C*H*$_2$), 1.44 (s, 3H, C-C*H*$_3$), 1.36-1.14 (m, 4H, C*H*$_2$), 0.97 (d, 3H, *J* = 6.5 Hz, CHC*H*$_3$), 0.90 (t, 3H, *J* = 7.1 Hz, C*H*$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9 (*C*=O), 137.3 (Ar*C*$_{ipso}$), 128.7 (2 x Ar*C*), 127.9 (Ar*C*), 125.5 (2 x Ar*C*), 99.9 (O-*C*-O), 87.6 (O*C*H$_2$-O), 73.1 (O*C*H$_2$), 70.6 (Ph*C*H), 59.1 (N*C*H), 41.1 (*C*CH$_3$), 34.0 (N*C*H$_3$), 33.7 (C-*C*H$_2$), 25.4 (*C*H$_2$), 23.8 (*C*H$_2$), 19.5 (C-*C*H$_3$), 14.2 (CH*C*H$_3$), 12.6 (CH$_2$*C*H$_3$). MS (APCI, pos.): *m*/*z* 348.3 $(M+H)^+$; HRMS (EI, pos.): *m*/*z* 347.2105 (347.2097 calc. for $C_{20}H_{29}NO_4$, (M^+)); 348.2172 (348.2175 calc. for $C_{20}H_{30}NO_4$ $(M+H)^+$).

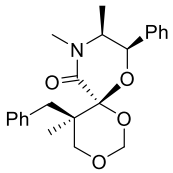
(5*R*,6*R*,8*R*,9*S*)-5-Isobutyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (117):



The reaction of alkene **97** (20 mg, 0.070 mmol), paraformaldehyde (0.35 mmol) in TFA (1 mL) for 18 h at 0 °C according to General Procedure 3 provided, after purification

by flash chromatography on silica gel (hexanes/EtOAc, 17:3), 19 mg (79%) of **117** as a white solid. R_f = 0.40 (hexanes/EtOAc, 1:1); mp = 92.6-94.2 °C; $[\alpha]_D^{20}$ = –67.1 (c 0.8, CH_2Cl_2); IR (neat): 2951, 2917, 2875, 1650, 1472, 1453, 1378, 1294, 1176, 1146, 1092, 1068, 972, 944 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.29 (m, 5H, Ar*H*), 5.41 (d, 1H, *J* = 3.1 Hz, C*H*Ph), 5.01 (d, 1H, *J* = 5.5 Hz, OC*H*$_2$O),), 4.95 (d, 1H, *J* = 5.5 Hz, OC*H*$_2$O), 4.08 (d, 1H, *J* = 10.7 Hz, C*H*$_2$OCH$_2$), 3.87 (d, 1H, *J* = 10.7 Hz, C*H*$_2$OCH$_2$), 3.49 (dq, 1H, *J* = 6.5, 3.1 Hz, C*H*CH$_3$), 3.01 (s, 3H, NC*H*$_3$), 1.82-1.67 (m, 1H, CH$_3$C*H*C*H*$_3$), 1.58 (dd, 1H, *J* = 14.1, 7.1 Hz, C*H*$_2$CH), 1.50 (s, 3H, C-C*H*$_3$), 1.31 (dd, 1H, *J* = 14.1, 4.4 Hz, C*H*$_2$CH), 0.98 (d, 3H, *J* = 6.5 Hz, C*H*$_3$CH), 0.95 (d, 3H, *J* = 2.9 Hz, (CH$_3$CHC*H*$_3$), 0.93 (d, 3H, *J* = 2.9 Hz, C*H*$_3$CHCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7 (N*C*=O), 137.2 (Ar*C*$_{ipso}$), 128.6 (2 × Ar*C*), 127.8 (Ar*C*), 125.4 (2 × Ar*C*), 100.1 (O-*C*-O), 87.4 (O*C*H$_2$O), 72.8 (O*C*H$_2$), 70.5 (Ph*C*H), 59.0 (*C*HCH$_3$), 42.7 (*C*H$_2$CH(CH$_3$)$_2$), 41.6 (^{i}Bu-*C*-CH$_3$), 33.9 (N*C*H$_3$), 25.8 ((CH$_3$)$_2$*C*H), 25.1 (CH$_3$CH*C*H$_3$), 23.5 (*C*H$_3$CHCH$_3$), 19.5 (^{i}Bu-C-*C*H$_3$), 12.7 (CH*C*H$_3$); MS (APCI, pos.): *m*/*z* 348.2 $(M+H)^+$ and 288.2 $((M-C_2H_4O_2)+H)^+$; HRMS (APPI, pos.): *m*/*z* 347.2103 (347.2097 calc. for $C_{20}H_{29}NO_4$ (M^+)) and 287.1887 (287.1885 calc. for $C_{18}H_{25}NO_2$ $(M-C_2H_4O_2)^+$).

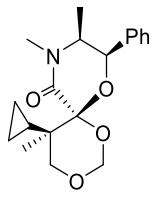
(5*R*,6*R*,8*R*,9*S*)-5-Benzyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (118):



The reaction of alkene **104** (22 mg, 0.060 mmol), paraformaldehyde (0.34 mmol) in TFA (1 mL) for 7 h at RT according to General Procedure 3 provided, after purification

by flash chromatography on silica gel (hexanes/EtOAc, 4:1), 19 mg (73%) of **118** as a white solid. R_f = 0.46 (hexanes/EtOAc, 1:1); mp = 152.7-153.9 °C; $[\alpha]_D^{20}$ = – 61.8 (c 1, CH_2Cl_2); IR (neat): 2983, 2969, 2891, 1644, 1482, 1455, 1397, 1364, 1291, 1209, 1176, 1132, 1084, 1026, 1003, 978, 948 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44-7.37 (m, 4H, Ar*H*), 7.36-7.21 (m, 6H, Ar*H*), 5.53 (d, 1H, *J* = 3.1 Hz, C*H*Ph), 5.29 (d, 1H, *J* = 5.5 Hz, OCH_2O), 5.08 (d, 1H, *J* = 5.5 Hz, OCH_2O), 3.96 (d, 1H, *J* = 11.0 Hz, CH_2OCH_2), 3.83 (d, 1H, *J* = 11.0 Hz, CH_2OCH_2), 3.55 (dq, 1H, *J* = 6.4, 3.1 Hz, C*H*CH_3), 3.35 (d, 1H, *J* = 13.1 Hz, PhCH_2), 3.05 (s, 3H, NCH_3), 2.76 (d, 1H, *J* = 13.1 Hz, PhCH_2), 1.14 (s, 3H, C-CH_3), 1.03 (d, 3H, *J* = 6.4 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1 (N*C*=O), 137.2 (ArC_{ipso}), 137.1 (ArC_{ipso}), 131.1 (2 × Ar*C*), 128.6 (2 × Ar*C*), 128.0 (2 × Ar*C*), 127.8 (Ar*C*), 126.3 (Ar*C*), 125.4 (2 × Ar*C*), 99.4 (O-*C*-C=O), 89.1 (OCH_2O), 70.7 (Ph*C*H), 70.2 (OCH_2), 58.9 (*C*HCH_3), 41.4 (Bn-*C*-CH_3), 38.6 (CH_2Ph), 33.8 (NCH_3), 18.0 (Bn-C-*C*H_3), 12.7 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 382.2 $(M+H)^+$; HRMS (EI, pos.): *m*/*z* 381.1952 (381.1940 calc. for $C_{23}H_{27}NO_4$ (M^+)).

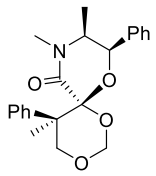
(5*R*,6*R*,8*R*,9*S*)-5-Cyclopropyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (119):



The reaction of alkene **105** (40 mg, 0.15 mmol), paraformaldehyde (0.74 mmol), conc. H_2SO_4 (2 drops) in acetic acid (1 mL) for 2 min. at 85 °C according to General Procedure 4 provided, after purification by flash chromatography on silica gel

(hexane/EtOAc, 7:3), 37 mg (77%) of **119** as a colorless liquid. R_f = 0.33 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ = –36.1 (c 0.8, CH_2Cl_2); IR (neat): 2980, 2927, 2882, 1660, 1452, 1384, 1292, 1206, 1164, 1127, 1095, 1065, 1031, 980, 961, 942, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.29 (m, 5H, Ar*H*), 5.42 (d, 1H, *J* = 3.1 Hz, PhC*H*), 5.08 (d, 1H, *J* = 5.6 Hz, OCH_2O), 4.90 (d, 1H, *J* = 5.6 Hz, OCH_2O), 4.21 (d, 1H, *J* = 10.5 Hz, OCH_2), 3.61 (d, 1H, *J* = 10.5 Hz, OCH_2), 3.51 (dq, 1H, *J* = 6.5, 3.1 Hz, C*H*CH_3), 3.01 (s, 3H, NCH_3), 1.13 (s, 3H, C-CH_3), 1.11-1.04 (m, 1H, C-C*H*), 1.01 (d, 3H, *J* = 6.5 Hz, CHCH_3), 0.40-0.23 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (*C*=O), 137.4 (ArC_{ipso}), 128.7 (2 x Ar*C*), 128.0 (Ar*C*), 125.5 (2 x Ar*C*), 100.3 (O-*C*-O), 87.2 (O*C*H_2O), 74.4 (O*C*H_2), 71.0 (Ph*C*H), 59.3 (*C*HCH_3), 40.6 (*C*CH_3), 34.1 (N*C*H_3), 15.1 (CH*C*H_3), 13.2 (C*C*H_3), 12.5 (C*C*H), -0.3 (*C*H_2CH_2), -0.4 (CH_2*C*H_2); MS (APCI, pos.): *m*/*z* 332.2 $(M+H)^+$ and 272.2 $(M-C_2H_4O_2+H)^+$; HRMS (APPI, pos.): *m*/*z* 331.1777 (331.1784 calc. for $C_{19}H_{25}NO_4$ (M^+)) and 271.1567 (271.1572 calc. for $C_{17}H_{21}NO_2$ $(M-C_2H_4O_2)^+$).

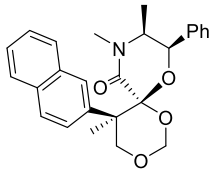
(5*R*,6*R*,8*R*,9*S*)-5,9,10-Trimethyl-5,8-diphenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (120):



The reaction of alkene **106** (270 mg, 0.880 mmol), paraformaldehyde (4.34 mmol) in TFA (4 mL) for 18 h at RT according to General Procedure 3 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 7:3), 295 mg (92%) of **120** as a white foam. R_f = 0.28 (hexane/EtOAc, 6:4); mp = 58.9-60.7 °C; $[\alpha]_D^{20}$ = +11.0 (c 1, CH_2Cl_2); IR (neat): 1656, 1493, 1448, 1383, 1238, 1161, 1091, 1029, 986 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 7H, Ar*H*), 7.24-7.16 (m, 3H, Ar*H*), 5.22 (d, 1H, *J* = 2.9 Hz, PhC*H*), 5.13 (d, 1H, *J* = 5.7 Hz, OCH_2O), 5.04 (d, 1H, *J* = 10.3 Hz, OCH_2), 4.91 (d, 1H, *J* = 5.7 Hz, OCH_2O), 3.82 (d, 1H, *J* = 10.3 Hz, OCH_2), 3.22 (dq, 1H, *J* = 6.6, 2.9 Hz, NC*H*), 2.93 (s, 3H, NCH_3), 2.04 (s, 3H, C-CH_3), -0.07 (d, 3H, *J* = 6.6 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (*C*=O), 142.1 (ArC_{ipso}), 136.9 (ArC_{ipso}), 128.5 (2 x Ar*C*), 128.2 (2 x Ar*C*), 127.8 (Ar*C*), 126.9 (2 x Ar*C*), 126.8 (Ar*C*), 125.4 (2 x Ar*C*), 99.8 (O-*C*-O), 86.8 (O*C*H_2O), 71.7 (O*C*H_2), 71.3 (Ph*C*H), 59.1 (NC*H*), 44.8 (Ph-*C*-CH_3), 33.8 (N*C*H_3), 22.2 (C-*C*H_3), 10.6 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 368.4 $(M+H)^+$; HRMS (CI, pos.): *m*/*z* 368.1862 (368.1862 calc. for $C_{22}H_{26}NO_4$ $(M+H)^+$).

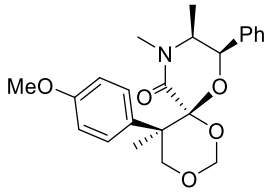
(5*R*,6*R*,8*R*,9*S*)-5,9,10-Trimethyl-5-(naphthalen-2-yl)-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (121):



The reaction of alkene **107** (41 mg, 0.11 mmol), paraformaldehyde (0.57 mmol), conc. H_2SO_4 (2 drops) in acetic acid (1 mL) for 20 min. at 85 °C according to General Procedure 4 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 7:3), 29 mg (60%) of **121** as a white solid. R_f = 0.34 (hexane/EtOAc, 1:1); mp = 142.3-144.1 °C; $[\alpha]_D^{20}$ = +56.6 (c 1, CH_2Cl_2); IR (neat): 2981, 2921, 2871, 1657, 1479, 1452, 1380, 1293, 1194, 1164, 1147, 1086, 1030, 993, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.72 (m, 4H, Ar*H*), 7.57-7.39 (m, 3H, Ar*H*), 7.37-7.12 (m, 5H, Ar*H*), 5.24 (d, 1H, *J* = 2.7 Hz, C*H*Ph), 5.18 (d, 1H, *J* = 5.5 Hz, OCH_2O), 5.16 (d, 1H, *J* = 10.3 Hz, CH_2OCH_2), 4.96 (d, 1H, *J* = 5.5 Hz, OCH_2O), 3.95 (d, 1H, *J* = 10.3 Hz, CH_2OCH_2), 3.18

(dq, 1H, J = 6.4, 2.7 Hz, C*H*CH_3), 2.93 (s, 3H, N-C*H*$_3$), 2.13 (s, 3H, C-C*H*$_3$), -0.28 (d, 3H, J = 6.4 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5 (N*C*=O), 139.8 (ArC_{ipso}), 137.0 (ArC_{ipso}), 133.4 (Ar*C*), 132.2 (Ar*C*), 128.6 (2 × Ar*C*), 128.1 (Ar*C*), 127.9 (Ar*C*), 127.7 (Ar*C*), 127.5 (Ar*C*), 126.2 (Ar*C*), 126.0 (2 × Ar*C*), 125.5 (2 × Ar*C*), 125.1 (Ar*C*), 100.1 (O-*C*-O), 87.1 (O*C*H_2O), 72.1 (O*C*H_2), 71.4 (Ph*C*H), 59.3 (*C*HCH_3), 45.1 (2-naphthyl-*C*-CH_3), 34.1 (N-*C*H_3), 22.6 (2-naphthyl-C-*C*H_3), 10.8 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 418.2 $(M+H)^+$ and 358.2 $(M-C_2H_4O_2+H)^+$; HRMS (APPI, pos.): *m*/*z* 417.1957 (417.1940 calc. for $C_{26}H_{27}NO_4$ (M^+)) and 357.1743 (357.1729 calc. for $C_{24}H_{23}NO_2$ $(M-C_2H_4O_2)^+$).

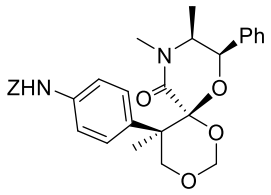
(5*R*,6*R*,8*R*,9*S*)-5-(4-Methoxyphenyl)-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (122):



To a solution of the alkene **108** (150 mg, 0.440 mmol) in glacial acetic acid (2 mL) at room temperature was added paraformaldehyde (66 mg, 2.2 mmol) followed by 6 drops of conc. H_2SO_4 and the reaction mixture was stirred for 20 h at room temparature. The acetic acid was removed under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (1 x 3 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 7:3) to provide 56 mg (32%) of **122** as a gum. R_f = 0.28 (hexane/EtOAc, 3:2); $[\alpha]_D^{20}$ = +38.7 (c 1, CH_2Cl_2); IR (neat): 2957, 2927, 1663, 1516, 1457, 1381, 1295, 1255, 1192, 1166, 1094, 1033, 988 cm^{-1}; ^{1}H

NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H, Ar*H*), 7.25-7.19 (m, 2H, Ar*H*), 6.86 (d, 2H, *J* = 8.9 Hz, Ar*H*), 5.23 (d, 1H, *J* = 2.9 Hz, C*H*Ph), 5.13 (d, 1H, *J* = 5.6 Hz, OCH_2O), 4.98 (d, 1H, *J* = 10.3 Hz, CH_2O), 4.91 (d, 1H, *J* = 5.6 Hz, OCH_2O), 3.78 (d, 1H, *J* = 10.3 Hz, CH_2O), 3.77 (s, 3H, OCH_3), 3.24 (dq, 1H, *J* = 6.5, 2.9 Hz, C*H*CH_3), 2.92 (s, 3H, NCH_3), 2.01 (s, 3H, Ar-C-CH_3), 0.01 (d, 3H, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (*C*=O), 158.3 (ArC_{ipso}), 137.0 (ArC_{ipso}), 134.2 (ArC_{ipso}), 128.5 (2 x Ar*C*), 128.0 (2 x Ar*C*), 127.8 (Ar*C*), 125.4 (2 x Ar*C*), 113.5 (2 x Ar*C*), 99.9 (O-*C*-O), 86.8 (OCH_2O), 71.9 (*C*H_2O), 71.3 (Ph*C*H), 59.1 (*C*HCH_3), 55.3 (O*C*H_3), 44.21 (CH_3-*C*-Ar), 33.9 (NCH_3), 22.3 (CH*C*H_3), 10.8 (*C*H_3-C-Ar); MS (APCI, pos.): *m*/*z* 398.2 $(M+H)^+$ and 338.2 $(M-C_2H_4O_2+H)^+$; HRMS (APPI, pos.): *m*/*z* 397.1907 (397.1889 calc. for $C_{23}H_{27}NO_5$ (M^+)) and 337.1694 (337.1678 calc. for $C_{21}H_{23}NO_3$ $(M-C_2H_4O_2)^+$).

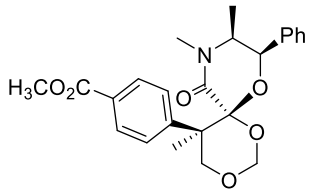
Benzyl-4-((5*R*,6*R*,8*R*,9*S*)-5,9,10-trimethyl-11-oxo-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-5-yl)phenylcarbamate (123):



The reaction of alkene **109** (53 mg, 0.11 mmol), paraformaldehyde (0.58 mmol), conc. H_2SO_4 (2 drops) in acetic acid (1 mL) for 50 min.at 85 °C according to General Procedure 4 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1), 34 mg (58%) of **123** as a colorless liquid. R_f = 0.29 (CH_2Cl_2/EtOAc, 85:15); $[\alpha]_D^{20}$ = +32.2 (c 0.6, CH_2Cl_2); IR (neat): 3291, 1730, 1650, 1598, 1529, 1453, 1406, 1323, 1295, 1216, 1194, 1165, 1090, 1066, 1031, 1012 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.41-7.27 (m, 12 H, Ar*H*), 7.23-7.18 (m, 2H, Ar*H*), 6.61 (br s, 1H, N*H*), 5.22 (d, 1H, *J* = 2.8 Hz, PhC*H*), 5.18 (s, 2H, OCH_2Ph), 5.12 (d, 2H, *J* = 5.6 Hz, OCH_2O), 4.98 (d, 1H, *J* = 10.3 Hz, CH_2O), 4.90 (d, 1H, *J* = 5.6 Hz, OCH_2O), 3.78 (d, 2H, *J* = 10.3 Hz, CH_2O), 3.24 (dq, 1H, *J* = 6.4, 2.8 Hz, C*H*CH_3), 2.91 (s, 3H, NCH_3), 2.00 (s, 3H, Ar-C-CH_3), 0.05 (d, 3H, *J* = 6.4 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (N*C*=O), 153.2 (N*C*O_2), 137.2 (Ar*C*$_{ipso}$), 136.9 (Ar*C*$_{ipso}$), 136.4 (Ar*C*$_{ipso}$), 135.9 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 128.5 (2 x Ar*C*), 128.4 (Ar*C*), 128.3 (2 x Ar*C*), 127.8 (Ar*C*), 127.6 (2 x Ar*C*), 125.4 (2 x Ar*C*), 118.1 (2 x Ar*C*), 99.8 (O-*C*-O), 86.8 (O*C*H_2O), 71.8 (O*C*H_2), 71.3 (Ph*C*H), 67.0 (Ph*C*H_2), 59.1 (*C*HCH_3), 44.4 (Ar-*C*-CH_3), 33.9 (N*C*H_3), 22.2 (Ar-*C*-*C*H_3), 10.9 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 517.2 $(M+H)^+$, 457.2 $(M-C_2H_4O_2+H)^+$ and $(M-PhCH_2)^+$; HRMS (APPI, pos.): *m*/*z* 516.2259 (516.2260 calc. for $C_{30}H_{32}N_2O_6$ (M^+)) and 456.2048 (456.2049 calc. for $C_{28}H_{28}N_2O_4$ $(M-C_2H_4O_2)^+$).

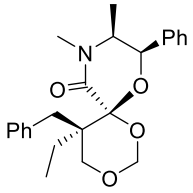
Methyl 4-((5*R*,6*R*,8*R*,9*S*)-5,9,10-trimethyl-11-oxo-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-5-yl)benzoate (124):



The reaction of alkene **110** (390 mg, 1.07 mmol), paraformaldehyde (5.34 mmol) in TFA (5 mL) for 4.5 days at room tempearature according to General Procedure 3 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 7:3), 389 mg (86%) of **124** as a white solid. R_f = 0.30 (hexane/EtOAc, 3:2); mp = 117.4-119.2 °C; $[\alpha]_D^{20}$ = +64.9 (c 1.1, CH_2Cl_2); IR (neat): 2989, 2941, 2892, 1705, 1652, 1447, 1394, 1283,

1188, 1154, 1087, 1020, 975 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07-8.03 (m, 2H, Ar*H*), 7.51-7.47 (m, 2H, Ar*H*), 7.43-7.32 (m, 3H, Ar*H*), 7.24-7.21 (m, 2H, Ar*H*), 5.29 (d, 1H, *J* = 3.0 Hz, C*H*Ph), 5.18 (d, 1H, *J* = 5.7 Hz, OC*H*$_2$O), 5.08 (d, 1H, *J* = 10.3 Hz, C*H*$_2$O), 4.98 (d, 1H, *J* = 5.7 Hz, OC*H*$_2$O), 3.95 (s, 3H, OCH_3), 3.90 (d, 1H, *J* = 10.3 Hz, C*H*$_2$O), 3.3 (dq, 1H, *J* = 6.6, 3.0 Hz, C*H*CH_3), 2.98 (s, 3H, NC*H*$_3$), 2.10 (s, 3H, Ar-C-C*H*$_3$), -0.01 (d, 3H, *J* = 6.6 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8 (*C*O_2CH_3), 164.0 (N-*C*=O), 147.6 (Ar*C*$_{ipso}$), 136.7 (Ar*C*$_{ipso}$), 129.4 (2 x Ar*C*), 128.5 (2 x Ar*C*), 128.5 (Ar*C*$_{ipso}$), 127.9 (2 x Ar*C*), 127.0 (2 x Ar*C*), 125.3 (2 x Ar*C*), 99.5 (O-*C*-O), 86.9 (O*C*H$_2$O), 71.6 (*C*H$_2$O), 71.3 (Ph*C*H), 59.1 (*C*HCH_3), 52.1 (O*C*H_3), 45.1 (Ar-*C*-CH_3), 33.9 (N*C*H_3), 22.1 (Ar-C-*C*H_3), 10.9 (CH*C*H_3); MS (APCI, pos.): *m*/*z* 426.2 $(M+H)^+$ and 366.2 $(M-C_2H_4O_2+H)^+$; HRMS (APPI, pos.): *m*/*z* 425.1838 (425.1838 calc. for $C_{24}H_{27}NO_6$ (M^+)).

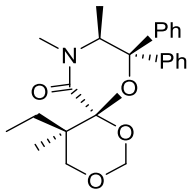
(5*R*,6*R*,8*R*,9*S*)-5-Benzyl-5-ethyl-9,10-dimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (125):



The reaction of alkene **111** (100 mg, 0.290 mmol), paraformaldehyde (1.49 mmol) in TFA (1.5 mL) for 30 h at 0 °C according to General Procedure 3 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 4:1), 83 mg (70%) of **125** as a white solid. R_f = 0.39 (EtOAc/hexane, 2:3); mp = 133.1-135.6 °C; $[\alpha]_D^{20}$ = –56.0 (c 1, CH_2Cl_2); IR (neat): 2989, 2912, 2884, 1642, 1482, 1454, 1204, 1177, 1130, 1092, 1015, 973, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.18 (m, 10H, Ar*H*), 5.69 (d, 1H,

J = 3.6 Hz, C*H*Ph), 5.31 (d, 1H, *J* = 5.6 Hz, OC*H*$_2$O), 5.08 (d, 1H, *J* = 5.6 Hz, OC*H*$_2$O), 4.23 (d, 1H, *J* = 12.0 Hz, C*H*$_2$OCH$_2$), 3.63 (d, 1H, *J* = 12.0 Hz, C*H*$_2$OCH$_2$), 3.57 (dq, 1H, *J* = 6.6, 3.6 Hz, C*H*CH$_3$), 3.30 (d, 1H, *J* = 13.1 Hz, PhC*H*$_2$), 3.03 (s, 3H, NC*H*$_3$), 3.01 (d, 1H, *J* = 13.1 Hz, PhC*H*$_2$), 1.66-1.45 (m, 2H, C*H*$_2$CH$_3$), 1.01 (d, 3H, *J* = 6.6 Hz, CHC*H*$_3$), 0.93 (t, 3H, *J* = 7.6 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.1 (N*C*=O), 137.9 (Ar*C*$_{ipso}$), 137.3 (Ar*C*$_{ipso}$), 131.1 (2 × Ar*C*), 128.5 (2 × Ar*C*), 128.0 (2 × Ar*C*), 127.7 (Ar*C*), 126.2 (Ar*C*), 125.5 (2 × Ar*C*), 99.0 (O-*C*-O), 89.4 (O*C*H$_2$O), 70.0 (*C*HPh), 68.7 (O*C*H$_2$), 58.6 (*C*HCH$_3$), 44.2 (Bn-*C*-Et), 35.2 (br, *C*H$_2$Ph), 33.7 (N*C*H$_3$), 23.4 (Bn-C-*C*H$_2$CH$_3$), 13.0 (CH*C*H$_3$), 9.4 (CH$_2$*C*H$_3$); MS (APCI, pos.): *m*/*z* 396.2 (M+H)$^+$ and 336.2 ((M-C$_2$H$_4$O$_2$)+H)$^+$; HRMS (APPI, pos.): *m*/*z* 395.2106 (395.2097 calc. for C$_{24}$H$_{29}$NO$_4$ (M$^+$)) and 335.1892 (335.1885 calc. for C$_{22}$H$_{25}$NO$_2$ (M-C$_2$H$_4$O$_2$)$^+$).

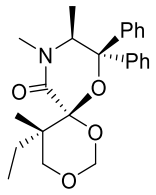
(5*R*,6*R*,9*S*)-5-Ethyl-5,9,10-trimethyl-8,8-diphenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (126):



The reaction of alkene **112** (37 mg, 0.11 mmol), paraformaldehyde (0.55 mmol) in TFA (1 mL) for 27 h at 0 °C according to General Procedure 3 provided, after purification by flash chromatography on silica gel (CH$_2$Cl$_2$/EtOAc, 95:5), 32 mg (73%) of **126** as a white solid. R_f = 0.36 (CH$_2$Cl$_2$/EtOAc, 96:4); mp = 200.7-202.3 °C; $[\alpha]_D^{20}$ = –317.8 (c 1, CH$_2$Cl$_2$); IR (neat): 2980, 2951, 1651, 1448, 1320, 1172, 1136, 1077, 1029, 997, 982, 953 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.38-7.08 (m, 10H, Ar*H*), 4.87 (d, 1H, *J* = 5.8 Hz, OC*H*$_2$O),

4.43 (d, 1H, J = 5.8 Hz, OCH_2O), 4.23 (q, 1H, J = 6.5 Hz, CHCH$_3$), 4.09 (d, 1H, J = 10.7 Hz, OCH_2), 3.69 (d, 1H, J = 10.7 Hz, OCH_2), 3.18 (s, 3H, NCH_3), 1.71 (ABX$_3$, 1H, J_{AB} = 13.7 Hz, J_{AX} = J_{BX} = 7.5 Hz, CH_2CH$_3$), 1.52 (ABX$_3$, 1H, J_{AB} = 13.7 Hz, J_{AX} = J_{BX} = 7.5 Hz, CH_2CH$_3$), 1.28 (s, 3H, C-CH_3), 0.98 (d, 3H, J = 6.5 Hz, CH_3CH), 0.86 (t, 3H, J = 7.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.7 (NC=O), 144.5 (ArC_{ipso}), 142.9 (ArC_{ipso}), 128.4 (2 × ArC), 128.3 (2 × ArC), 128.0 (ArC), 127.9 (2 × ArC), 127.3 (ArC), 125.8 (2 × ArC), 99.3 (O-C-O), 87.4 (OCH$_2$O), 79.9 (CPh$_2$), 72.2 (OCH$_2$), 59.7 (CHCH$_3$), 41.9 (Et-C-CH$_3$), 34.2 (NCH$_3$), 26.9 (CH$_2$CH$_3$), 19.0 (Et-C-CH$_3$), 16.0 (CHCH$_3$), 8.0 (CH$_2C$H$_3$); MS (APCI, pos.): m/z 396.2 (M+H)$^+$ and 336.2 (M-C$_2$H$_4$O$_2$+H)$^+$; HRMS (APPI, pos.): m/z 395.2106 (395.2097 calc. for C$_{24}$H$_{29}$NO$_4$ (M$^+$)) and 335.1891 (335.1885 calc. for C$_{22}$H$_{25}$NO$_2$ (M-C$_2$H$_4$O$_2$)$^+$).

(5S,6R,9S)-5-Ethyl-5,9,10-trimethyl-8,8-diphenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (127):



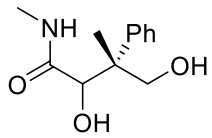
The reaction of alkene **114** (50 mg, 0.15 mmol), paraformaldehyde (0.75 mmol) in TFA (1 mL) for 42 h at 0 °C according to General Procedure 3 provided crude **105** (dr = 5:1). Purification by flash chromatography on silica gel (CH$_2$Cl$_2$/EtOAc, 98:2) provided 42 mg (71%) of **127** as a single diaseteromer (white solid). R_f = 0.29 (CH$_2$Cl$_2$/EtOAc, 96:4); mp. = 152.3-153.9 °C; $[\alpha]_D^{20}$ = –349.1 (c 1.2, CH$_2$Cl$_2$); IR (neat): 2971, 2924, 2883, 1660, 1635, 1449, 1155, 1117, 1080, 1017, 986, 960, 945 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ

7.36-7.11 (m, 10H, Ar*H*), 4.85 (d, 1H, *J* = 5.7 Hz, OC*H*$_2$O), 4.55 (d, 1H, *J* = 5.7 Hz, OC*H*$_2$O), 4.25 (q, 1H, *J* = 6.5 Hz, C*H*CH$_3$), 3.93 (AB system, 2H, $\Delta\nu_{AB}$ = 12.9 Hz J_{AB}= 11.2 Hz, OC*H*$_2$), 3.17 (s, 3H, NC*H*$_3$), 2.05 (ABX$_3$, 1H, J_{AB} = 14.1 Hz, J_{AX} = J_{BX} = 7.4 Hz C*H*$_2$CH$_3$), 1.53 (ABX$_3$, 1H, J_{AB} = 14.1 Hz, J_{AX} = J_{BX} = 7.4 Hz, C*H*$_2$CH$_3$), 1.08 (s, 3H, C-C*H*$_3$), 0.99 (d, 3H, *J* = 6.5 Hz, C*H*$_3$CH), 0.84 (t, 3H, *J* = 7.4 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.8 (N*C*=O), 144.4 (Ar*C*$_{ipso}$), 142.8 (Ar*C*$_{ipso}$), 128.3 (2 × Ar*C*), 128.1 (2 × Ar*C*), 127.79 (Ar*C*), 127.76 (2 × Ar*C*), 127.1 (Ar*C*), 125.7 (2 × Ar*C*), 99.3 (O-*C*-O), 87.6 (O*C*H$_2$O), 79.9 (*C*Ph$_2$), 69.5 (O*C*H$_2$), 59.4 (*C*HCH$_3$), 41.7 (Et-*C*-CH$_3$), 34.0 (N*C*H$_3$), 25.6 (*C*H$_2$CH$_3$), 18.1 (Et-C-*C*H$_3$), 15.9 (CH*C*H$_3$), 7.9 (*C*H$_3$CH$_2$); MS (APCI, pos.): *m*/*z* 396.2 (M+H)$^+$ and 336.2 (M-C$_2$H$_4$O$_2$+H)$^+$; HRMS (APPI, pos.): *m*/*z* 395.2108 (395.2097 calc. for C$_{24}$H$_{29}$NO$_4$ (M$^+$)) and 335.1893 (335.1885 calc. for C$_{22}$H$_{25}$NO$_2$ (M-C$_2$H$_4$O$_2$)$^+$).

Procedure for the synthesis of 138 and 139:

To anhydrous liquid ammonia (distilled over sodium) was added sodium metal at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of the Prins product in anhydrous THF and the mixture was stirred at -78 °C. A mixture of MeOH/H$_2$O (3:1, 2 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 8 h (for **139**) or for 30 min (for **138**). For **138**, the resulting solution was diluted with water and extracted with ethylacetate. For **139**, the aqueous solution was extracted with ethyl acetate and then acidified with aqueous 1.0 N HCl. Extraction of the acidic solution with ethyl acetate provided the crude product.

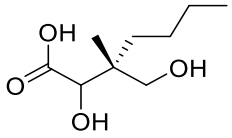
(3*R*)-2,4-Dihydroxy-*N*,3-dimethyl-3-phenylbutanamide (138):



Reduction of **120** (250 mg, 0.680 mmol) in anhydrous THF (2 mL) with sodium (94 mg, 4.1 mmol) in liquid ammonia (6 mL) for 10 min followed by addition of MeOH/H_2O and stirring at ambient temperature for 30 min., the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:8) to provide 59 mg of major diastereomer and 28 mg of minor diastereomer (56% combined yield of the two isomers) of the α-hydroxyamide **138** (dr = 2:1) as a colorless gum. Major diastereomer: R_f = 0.24 (hexanes/EtOAc, 1:9); $[\alpha]_D^{20}$ = –31.5 (c 1, CH_2Cl_2); IR (neat): 3353 (br), 2932, 1645, 1539, 1453, 1408, 1290, 1246, 1159, 1085, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47-7.38 (m, 4H, Ar*H*), 7.35-7.29 (m, 1H, Ar*H*), 5.05 (br s, 1H, N*H*), 4.52 (br s, 1H, C*H*OH), 4.12 (d, 1H, *J* = 11.3, OCH_2), 3.82 (s, 1H, O*H*), 3.65 (d, 1H, *J* = 11.3, OCH_2), 3.10 (s, 1H, O*H*), 2.63 (d, 3H, *J* = 4.9, NCH_3), 1.40 (s, 3H, C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6 (*C*=O), 141.9 (ArC_{ipso}), 129.1 (2 x Ar*C*), 127.6 (Ar*C*), 126.9 (2 x Ar*C*), 76.9 (Ph*C*H), 70.7 (O*C*H_2), 47.2 (Ph-*C*), 26.2 (N*C*H_3), 16.7 (C-*C*H_3); MS (CI, pos.): *m*/*z* 206.1 (M-OH); 224.1 $(M+H)^+$; HRMS (CI, pos.): *m*/*z* 224.1292 (224.1287 calc. for $C_{12}H_{18}NO_3$ $(M+H)^+$); Minor diastereomer: R_f = 0.25 (hexanes/EtOAc, 1:9); $[\alpha]_D^{20}$ = – 52.2 (c 1, CH_2Cl_2); IR (neat): 3351 (br), 2935, 1643, 1541, 1455, 1409, 1371, 1247, 1155, 1081, 1028, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H, Ar*H*), 7.41-7.36 (m, 2H, Ar*H*), 7.32-7.29 (m, 1H, Ar*H*), 6.80 (br s, 1H, N*H*), 4.59 (br s, 1H, C*H*OH), 4.32-4.29 (br t, 1H, *J* = 5.8, O*H*), 4.00 (br dd, 1H, *J* = 3.3, 11.5, OCH_2), 3.64 (br dd, 1H, *J* = 5.5, 11.5, OCH_2), 2.87 (d, 3H, *J* =

5.0, NCH_3), 1.60 (br s, 1H, OH), 1.30 (s, 3H, C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (*C*=O), 143.6 (ArC_{ipso}), 129.0 (2 x Ar*C*), 127.3 (Ar*C*), 126.6 (2 x Ar*C*), 77.0 (C(O)*C*H), 70.3 (O*C*H_2), 47.8 (Ph-*C*), 25.8 (N*C*H_3), 15.8 (C*C*H_3); HRMS (APPI, pos.): *m*/*z* 223.1214 (223.1208 calc. for $C_{12}H_{17}NO_3$ $(M)^+$).

(*R*)-2-Hydroxy-3-(hydroxymethyl)-3-methylheptanoic acid (139):



Reduction of **116** (250 mg, 0.720 mmol) in anhydrous THF (2.5 mL) with sodium (99 mg, 4.3 mmol) in liquid ammonia (6 mL) for 10 min followed by addition of MeOH/H_2O and stirring at ambient temperature for 8 h provided 118 mg (86%) of the α-hydroxy carboxylic acid **139** (dr = 1:1) as a colorless liquid. R_f = 0.39 (hexane/EtOAc, 3:2); IR (neat): 3431, 2958, 2932, 2872, 2862, 1763, 1459, 1185, 1111, 1092, 999 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (d, 1H, *J* = 9.1 Hz, CH_2OH), 4.18 (s, 1H, C*H*OH), 4.14 (s, 1H, C*H*OH), 3.99 (AB system, 2H, $\Delta\nu_{AB}$ = 14.7 Hz, *J* = 9.0 Hz, CH_2OH), 3.87 (d, 1H, *J* = 9.1 Hz, CH_2OH), 3.59 (br s, 1H, CO_2H), 1.67-1.22 (m, 12H, CH_2), 1.20 (s, 3H, C-CH_3), 1.08 (s, 3H, C-CH_3), 0.92 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 0.91 (t, 3H, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.11 (*C*=O), 178.06 (*C*=O), 76.0 (*C*HOH), 75.9 (*C*H_2OH), 75.4 (*C*HOH), 74.2 (*C*H_2OH), 43.9 (*n*Bu-*C*-CH_3), 43.4 (*n*Bu-*C*-CH_3), 37.4 (*C*H_2), 31.2 (*C*H_2), 26.4 (*C*H_2), 26.1 (*C*H_2), 23.3 (*C*H_2), 23.2 (*C*H_2), 21.5 (*C*H_3), 16.5 (*C*H_3), 14.0 (*C*H_3), 13.9 (*C*H_3); MS (APCI, neg.): *m*/*z* 189.0 (M-H); HRMS (APPI, neg.): *m*/*z* 190.1198 (190.1205 calc. for $C_9H_{18}O_4$ $(M)^-$).

General procedure for conversion of the Prins products into *β*-hydroxy carboxylic acids:

To anhydrous liquid ammonia (distilled over sodium) was added sodium metal at −78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of the Prins product in anhydrous THF and the mixture was stirred at -78 °C. A mixture of MeOH/H_2O (3:1, 2 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 8-9 h. Water (2 mL) was added and the mixture was extracted with ethylacetate (1 x 10 mL). The aqueous layer was acidified to pH ~4 with 1M HCl and the mixuture was extracted with ethyl acaetate. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide the hydroxy carboxylic acid. This was used in the next step without purification.

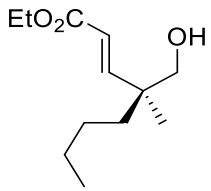
To a stirred solution of the hydroxy carboxylic acid in THF at 0 ºC was added a solution of BH_3·THF (1M solution in THF) and the mixture was stirred at room temperature until complete consumption of the acid (TLC). The mixture was cooled to 0 °C, acidified with aqueous HCl (1M, 2 mL), stirred at room temperature for 15 min and then extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with aq. NaOH (10%) followed by brine and then dried over Na_2SO_4 and concentrated under reduced pressure to provide the product triol. This was used in the next step without purification.

To a stirred solution of the triol in MeOH/H_2O (100/1) at 0 ºC was added $NaIO_4$. The mixture was stirred at room temperature until complete consumption of the triol (TLC) and cold, aqueous saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3 x 15 mL) and the combined extracts were washed with brine, dried over

Na_2SO_4 and concentrated under reduced pressure to provide the product aldehyde. This was used in the next step without purification.

To a solution of the aldehyde in *t*-butyl alcohol were added a solution of 2-methyl-2-butene (2M solution in THF) followed by a solution of $NaClO_2$ and NaH_2PO_4 in H_2O (1 mL). The resulting solution was stirred at room temperature and the mixture was then concentrated under reduced pressure. The residue was treated with aq. NaOH (10%, 2 mL), the mixture was stirred at room temperature for 30 min and then extracted with ethyl acetate (1 x 10 mL). The aqueous layer was acidified to pH ~4 with aqueous HCl (1.0 M, 2 mL) and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure provide the pure hydroxy carboxylic acid.

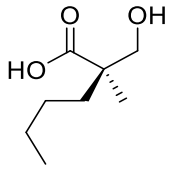
(*S*,*E*)-Ethyl 4-(hydroxymethyl)-4-methyloct-2-enoate (142):



This was prepared from **116** by adaptation of the general procedure upto the aldehyde stage. Reduction of the Prins product **116** (250 mg, 0.720 mmol) in anhydrous THF (2.5 mL) with sodium (99 mg, 4.3 mmol) in liquid ammonia (6 mL) for 10 min followed by addition of MeOH/H_2O and stirring at ambient temperature for 8 h provided 118 mg (86%) of the α-hydroxy carboxylic acid as a colorless liquid. Reduction of this acid (89 mg, 0.47 mmol) in THF (2 mL) with BH_3·THF (4.7 mL, 1.0 M solution in THF, 4.7 mmol) for 37 h provided 76 mg (93%) of the product triol as a colorless liquid. Oxidative

cleavage of the triol (76 mg, 0.43 mmol) with $NaIO_4$ (369 mg, 1.73 mmol) in MeOH/H_2O (100/1, 3 mL) for 3 h, provided 53 mg (85%) of the aldehyde as a colorless liquid. The aldehyde was subjected to a Horner-Wadsworth-Emmons reaction. Reaction of the aldehyde (62 mg, 0.43 mmol) in acetonitrile (1 mL) with triethylphosphonoacetate (0.13 mL, 0.64 mmol) and DBU (96 µL, 0.64 mmol) at ambient temperature for 3 h gave after purification by flash chromatography on silica gel (hexane/EtOAc, 4:1), 49 mg (53%) of **142** as a colorless liquid. R_f = 0.31 (hexane/EtOAc, 7:3); $[\alpha]_D^{20}$ = +9.1 (c 1.2, CH_2Cl_2); IR (neat): 3444, 2958, 2931, 2872, 2862, 1715, 1700, 1648, 1465, 1367, 1309, 1269, 1180, 1034, 991 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, 1H, *J* = 16.0 Hz, *H*C=CHCO$_2$Et), 5.81 (d, 1H, *J* =16.0 Hz, HC=C*H*CO$_2$Et), 4.19 (q, 2H, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 3.46 (AB system, 2H, $\Delta\nu_{AB}$ = 20.0 Hz *J* = 10.7 Hz, C*H*$_2$OH), 1.49-1.09 (m, 6H, C*H*$_2$), 1.30 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.06 (s, 3H, CC*H*$_3$), 0.89 (t, 3H, *J* = 7.0 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.8 (C-*C*=O), 154.5 (H*C*=CHCO$_2$Et), 120.7 (HC=*C*HCO$_2$Et), 69.8 (*C*H$_2$OH), 60.4 (O*C*H$_2$CH$_3$), 42.4 (CH$_3$-*C*-*n*Bu), 36.7 (C-*C*H$_2$), 26.0 (*C*H$_2$), 23.4 (*C*H$_2$), 19.8 (C-*C*H$_3$), 14.3 (*C*H$_3$), 14.0 (*C*H$_3$); MS (APCI, pos.): *m*/*z* 215.1 $(M+H)^+$, 197.1 $(M-OH)^+$ and 169.1 $(M-OC_2H_5)^+$; HRMS (APPI, pos.): *m*/*z* 214.1566 (214.1569 calc. for $C_{12}H_{22}O_3$ (M^+)).

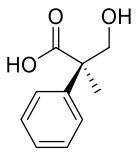
(*R*)-2-(Hydroxymethyl)-2-methylhexanoic acid (146):



This was prepared from **116** by adaptation of the general procedure upto the aldehyde stage. Oxidation of the aldehyde (52 mg, 0.36 mmol) with $NaClO_2$ (130 mg, 1.44

mmol) and NaH_2PO_4 (172 mg, 1.44 mmol) in 1 mL H_2O, *t*-butyl alcohol (3 mL), 2-methyl-2-butene (1.8 mL, 2.0 M solution in THF, 3.6 mmol) and for 15 h provided 35 mg (61%) of the carboxylic acid **146** as a colorless liquid. R_f = 0.29 (hexane/EtOAc, 7:3); $[\alpha]_D^{20}$ = –14.5 (c 0.8, $CHCl_3$); IR (neat): 3439 (br), 2929, 1699, 1461, 1407, 1381, 1282, 1220, 1160, 1032 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.0-5.5 (br, CO_2H), 3.75 (d, 1H, *J* = 9.5 Hz, OCH_2), 3.52 (d, 1H, *J* = 9.5 Hz, OCH_2), 1.69-1.53 (m, 2H, CH_2), 1.30-1.26 (m, 4H, CH_2) 1.22 (s, 3H, C-CH_3), 0.90 (t, 3H, *J* = 6.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9 (*C*=O), 68.0 (OCH_2), 47.7 (*C*-C=O), 35.5 (C-CH_3), 26.3 (CH_2), 23.2 (CH_2), 19.4 (CH_2), 13.9 (CH_2CH_3); MS (APCI, neg.): *m*/*z*159.1 $(M-H)^-$; HRMS (CI neg.): *m*/*z*159.1028 (159.1021 calc. for $C_8H_{15}O_3$ $(M-H)^-$.

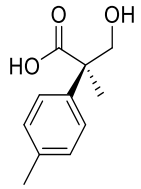
(*R*)-3-Hydroxy-2-methyl-2-phenylpropanoic acid (147):



Prepared according to the general procedure. Reduction of the Prins product **120** (185 mg, 0.500 mmol) in anhydrous THF (1.5 mL) with sodium (103 mg, 4.50 mmol) in liquid ammonia (5 mL) for 10 min followed by addition of $MeOH/H_2O$ and stirring at ambient temperature for 8 h provided 75 mg (71%) of the α-hydroxy carboxylic acid (dr =3.5:1) as a colorless liquid. Reduction of this acid (60 mg, 0.28 mmol) in THF (1 mL) with BH_3·THF (2.85 mL, 1.00 M solution in THF, 2.85 mmol) for 27 h provided 42 mg (75%) of the product triol as a colorless liquid. Oxidative cleavage of the triol (39 mg, 0.19 mmol) with $NaIO_4$ (170 mg, 0.790 mmol) in $MeOH/H_2O$ (100/1, 2 mL) for 3 h, provided 28 mg (87%) of the aldehyde as a colorless liquid. Oxidation of the aldehyde (27 mg, 0.16

mmol) with $NaClO_2$ (59 mg, 0.65 mmol) and NaH_2PO_4 (78 mg, 0.65 mmol) in 1 mL H_2O, *t*-butyl alcohol (2 mL), 2-methyl-2-butene (0.80 mL, 2.0 M solution in THF, 1.6 mmol) and for 12 h provided 22 mg (74%) of the carboxylic acid **147** as a colorless liquid. R_f = 0.24 (hexane/EtOAc, 65:35); $[\alpha]_D^{20}$ = +23.6 (c 1.9, EtOH), lit.[17] $[\alpha]_D^{20}$ = +26.6 (c 2, EtOH), IR (neat): 3061 (br), 1701, 1498, 1454, 1379, 1254, 1157, 1122, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H, Ar*H*), 4.12 (d, 1H, *J*= 11.5 Hz, OCH_2), 3.70 (d, 1H, *J* = 11.5 Hz, OCH_2), 1.70 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.9 (*C*=O), 139.6 (ArC_{ipso}), 128.7 (2 x Ar*C*), 127.7 (Ar*C*), 126.3 (2 x Ar*C*), 69.1 (OCH_2), 52.4 (Ph-*C*), 20.1 (C-*C*H_3); MS (APCI, neg.): *m*/*z* 179.1 $(M–H)^-$; HRMS (CI pos.): *m*/*z* 181.0872 (181.0865 calc. for $C_{10}H_{13}O_3$ $(M+H)^+$).

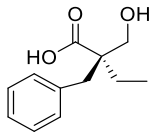
(*R*)-3-Hydroxy-2-methyl-2-p-tolylpropanoic acid (148):



Prepared according to the general procedure. Reduction of the Prins product **115** (150 mg, 0.33 mmol) in anhydrous THF (2 mL) with sodium (45 mg, 2.0 mmol) in liquid ammonia (5 mL) for 3 min. followed by addition of MeOH/H_2O and stirring at ambient temperature for 9 h provided 59 mg (81%) of the α-hydroxy carboxylic acid (single diastereomer) as a white foam. Reduction of this acid (35 mg, 0.15 mmol) in THF (1 mL) with BH_3·THF (1.56 mL, 1.00 M solution in THF, 1.56 mmol) for 47 h provided 30 mg (91%) of the product triol as a colorless liquid. Oxidative cleavage of the triol (30 mg, 0.14 mmol) with $NaIO_4$ (122 mg, 0.570 mmol) in MeOH/H_2O (100/1, 2 mL) for 3 h, provided

24 mg (96%) of the aldehyde as a colorless liquid. Oxidation of the aldehyde (24 mg, 0.13 mmol) with $NaClO_2$ (49 mg, 0.54 mmol) and NaH_2PO_4 (65 mg, 0.54 mmol) in 1 mL H_2O, *t*-butyl alcohol (2 mL), 2-methyl-2-butene (0.670 mL, 2.00 M solution in THF, 1.34 mmol) and for 15 h provided 19 mg (73%) of the carboxylic acid **148** as a white solid. R_f = 0.40 (hexane/EtOAc, 1:1); mp = 103.8-104.9 °C; $[\alpha]_D^{20}$ = +31.2 (c 0.7, $CHCl_3$), lit.[18] $[\alpha]_D^{20}$ = –39 (c 1, $CHCl_3$) for the *S* enantiomer); IR (neat): 3423, 2981, 2923, 2636, 1700, 1514, 1455, 1393, 1264, 1250, 1208, 1195, 1031, 1018 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.15 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.00 (d, 2H, *J* = 8.1 Hz, Ar*H*), 3.98 (d, 1H, *J* = 10.6 Hz, C*H*$_2$OH), 3.57 (d, 1H, *J* = 10.6 Hz, C*H*$_2$OH), 3.40-2.40 (br, CO_2H), 2.16 (s, 3H, ArC*H*$_3$), 1.45 (s, 3H, C-C*H*$_3$); ^{13}C NMR (75 MHz, acetone-d_6): δ 176.7 (*C*=O), 139.8 (Ar*C*$_{ipso}$), 137.0 (Ar*C*$_{ipso}$), 129.7 (2 × Ar*C*), 127.1 (2 × Ar*C*), 69.2 (*C*H$_2$OH), 52.7 (CH$_3$-*C*-Ar), 21.1 (Ar*C*H$_3$ or *C*H$_3$-C-Ar), 20.9 (Ar*C*H$_3$ or *C*H$_3$-C-Ar); MS (APCI, neg.): *m*/*z* 193.0 $(M-1)^-$; HRMS (APPI, neg.): *m*/*z* 194.0955 (194.0943 calc. for $C_{11}H_{14}O_3$ (M^-)).

(*R*)-2-Benzyl-2-(hydroxymethyl)butanoic acid (149):



Prepared according to the general procedure. Reduction of the Prins product **125** (120 mg, 0.300 mmol) in anhydrous THF (4 mL) with sodium (104 mg, 4.54 mmol) in liquid ammonia (7 mL) for 35 min followed by addition of MeOH/H_2O and stirring at ambient temperature for 8 h provided 55 mg (90%) of the α-hydroxy carboxylic acid (dr = 1.4:1) as a colorless liquid. Reduction of this acid (50 mg, 0.21 mmol) in THF (2 mL) with BH_3·THF (2.1 mL, 1.0 M solution in THF, 2.1 mmol) for 50 h provided 45 mg (95%) of

the product triol as a colorless liquid. Oxidative cleavage of the triol (44 mg, 0.19 mmol) with $NaIO_4$ (168 mg, 0.780 mmol) in MeOH/H_2O (100/1, 2 mL) for 6 h, provided 35 mg (94%) of the aldehyde as a colorless liquid. Oxidation of the aldehyde (34 mg, 0.17 mmol) with $NaClO_2$ (64 mg, 0.70 mmol) and NaH_2PO_4 (84 mg, 0.70 mmol) in 1 mL H_2O, *t*-butyl alcohol (2 mL), 2-methyl-2-butene (0.88 mL, 2.0 M solution in THF, 1.8 mmol) and for 12 h provided 28 mg (76%) of the carboxylic acid **149** as a white solid. R_f = 0.44 (hexane/EtOAc, 1:1); mp = 97.8-99.3 °C; $[\alpha]_D^{20}$ = –15.1 (c 1, MeOH); IR (neat): 3436, 3029, 2967, 2920, 2881, 1710, 1694, 1382, 1316, 1210, 1157, 1133, 1053, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.19 (m, 5H, Ar*H*), 7.00-5.90 (br, CO_2H), 3.74 (d, 1H, *J* = 11.4 Hz, CH_2OH), 3.53 (d, 1H, *J* = 11.4 Hz, CH_2OH), 3.14 (d, 1H, *J* = 13.4 Hz, PhCH_2), 2.89 (d, 1H, *J* = 13.4 Hz, PhCH_2), 1.73 (ABX_3, 1H, J_{AB} = 14.4 Hz, J_{AX} = J_{BX} = 7.3 Hz, CH_3CH_2), 1.54 (ABX_3, 1H, J_{AB} = 14.4 Hz, J_{AX} = J_{BX} = 7.3 Hz, CH_3CH_2), 0.93 (t, 3H, *J* = 7.3 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9 (*C*=O), 136.6 (ArC_{ipso}), 130.3 (2 × Ar*C*), 128.2 (2 × Ar*C*), 126.7 (Ar*C*), 63.2 (CH_2OH), 52.5 (Et-*C*-Bn), 38.4 ($PhCH_2$), 26.1 (CH_3CH_2), 8.7 (CH_3CH_2); MS (APCI, neg.): *m*/*z* 207.0 $(M-1)^-$; HRMS (APPI, neg.): *m*/*z* 208.1093 (208.1099 calc. for $C_{12}H_{16}O_3$ (M^-)).

1.8 References

1. (a) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740. (b) Khan, A.; Zhang, Y. J. *Synlett* **2015**, *26*, 853. (c) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181. (d) Repka, L. M.; Reisman, S. E. *J. Org. Chem.* **2013**, *78*, 12314. (e) Bella, M.; Gasperi, T. *Synthesis*, **2009**, 1583. (f) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (g) Christoffers, J.; Barro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473.
2. (a) Penrose, S. D.; Scott, A. J.; Breccia, P.; Haughan, A. F.; Burli, R. W.; Jarvis, R. E.; Dominguez, C. *Org. Lett.* **2015**, *17*, 1401. (b) watson, C. G.; Balanta, A.; Elford, T. G.; Essafi, S.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2014**, *136*, 17370. (c) Minko, Y.; Marek, I. *Chem. Commun.* **2014**, *50*, 12597. (d) Minko, Y.; Pasco, M.; Lercher, L.; Marek, I. *Nat. Protoc.* **2013**, *8*, 749. (e) Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, *8*, 1359. (f) Tiong, E. A.; Gleason, J. L. *Org. Lett.* **2009**, *11*, 1725. (g) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.*, **2012**, *51*, 4568. (h) Allais, C.; Tsai, A. S.; Nuhant, P.; Roush, W. R. *Angew. Chem., Int. Ed.*, **2013**, *52*, 12888.
3. Selected recent reports: (a) Alberch, E.; Brook, C.; Asad, S. A.; Shevryev, M.; Ulicki, J. S.; Hossain, M. M. *Synlett* **2015**, *26*, 388. (b) Guo, X.; Dai, Y.; Guo, T.; Franchino, A.; Dixon, D. J.; Ye, J. *Org. Lett.* **2015**, *17*, 1505. (c) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340. (d) Badiola, E.; Fser, B.; Gomez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; Garcia, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869. (d) Zhu, Y.; Zhang, L.; Luo, S. *J. Am.*

Chem. Soc. **2014**, *136*, 14642. (e) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11257.

4. (a) Turnbull, B. W. H.; Evans, P. A. *J. Am. Chem. Soc.* **2015**, *137*, 6156. (b) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593.

5. (a) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120. (b) 5. Pansare, S. V.; Bhattacharyya, A. *Tetrahedron* **2003**, *59*, 3275. (c) Sunil V. Pansare, S.V.; Adsool, V.A. *Org. Lett.* **2006**, *8*, 2035. (d) (a) Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 5879.

6. Prepared from *S*-methyl alaninate by adaptation of the reported procedure; Aratani, T.; Hazama, M.; Yoneyoshi, Y.; Suzukamo, G. *Eur. Pat. Appl.* **1983** EP 75868 A2 19830406.

7. (a) Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011 (b) Pansare research group, Kulkarni, K. G., Ph.D. Dissertation, Memorial University, **2014**

8. Solladié, G.; Berl V. *Synlett* **1991**, 795.

9. Details of the synthesis and characterization of ***E*-86**, ***E*-87** and ***E*-96** are provided in the Experimental Section.

10. Negishi and Kumada cross-coupling reactions and optimization of Suzuki-Miyaura cross-coupling with arylboronic acids was studied by Rakesh Thorat in the Pansare group. Thorat, R. G., Ph.D. Dissertation, Memorial University, **2014**.

11. (a) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (b) St. Denis, J. D.; Scully, C. C. G.; Frank Lee, C.; Yudin, A. K. *Org. Lett.* **2014**, *16*, 1338.

12. (a) Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron* **2007**, *63*, 768. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

13 (a) Greco, S. J.; Fiorot, R. G.; Lacerda Jr. V.; dos Santos, R. B. *Aldrichim. Acta* **2013**, *46*, 59. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925. (c) Pansare, S. V.; Jain, R. P. *Org. Lett.* **2000**, *2*, 175.

14. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

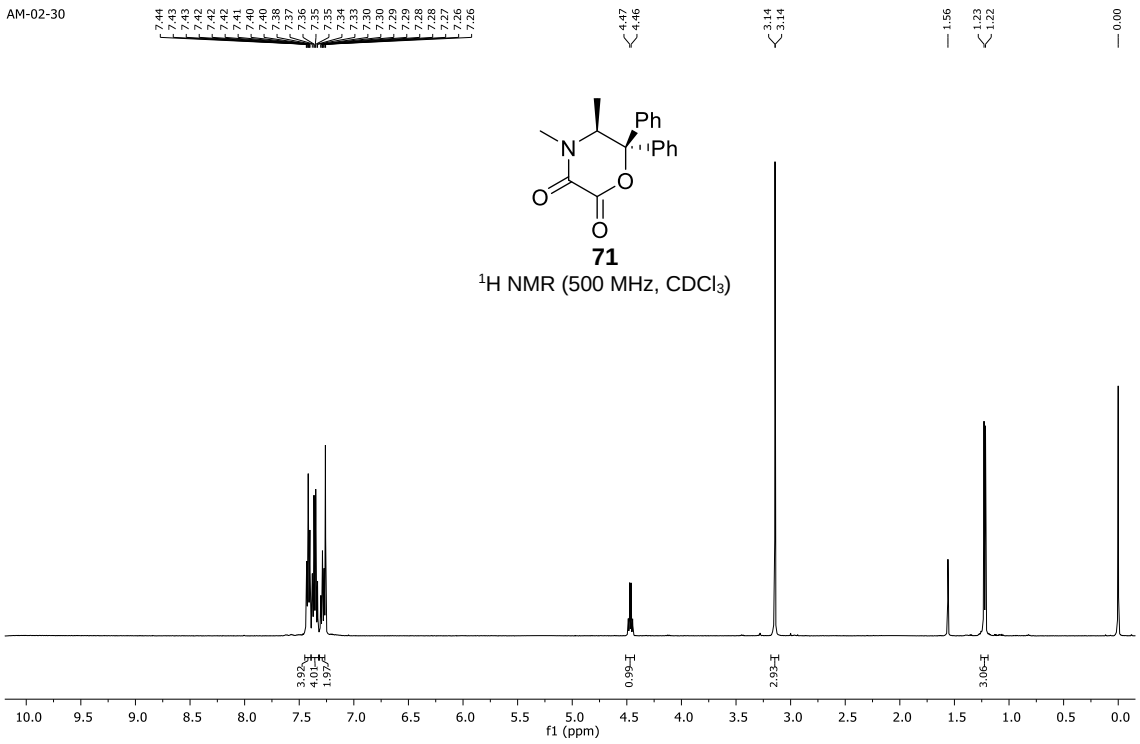
15 Dioubankova, N. N.; Malakhov, A. D.; Stetsenko, D. A.; Korshun, V. A.; Gait, M. J. *Org. Lett.* **2002**, *4*, 4607.

16 (a) Awuah, E.; Ma, E.; Hoegl, A.; Vong, K.; Habib, E.; Auclair, K. *Biorg. Med. Chem. Lett.* **2014**, *22*, 3083. (b) Hoegl, A.; Darabi, H.; Tran, E.; Awuah, E.; Kerdo, E. S. C.; Habib, E.; Saliba, K. J. Auclair. K. *Biorg. Med. Chem. Lett.* **2014**, *24*, 3274.

17. Lu, M. C.; Shih, L. B.; Jae, H. S.; Gearien, J. E.; Thompson, E. B. *J. Med. Chem.* **1987**, *30*, 424.

18. Canet, J.-L.; Fadel, A.; Salaün, J. *J. Org. Chem.* **1992**, *57*, 3463.

1.9 Selected ^{1}H NMR and ^{13}C NMR Spectra



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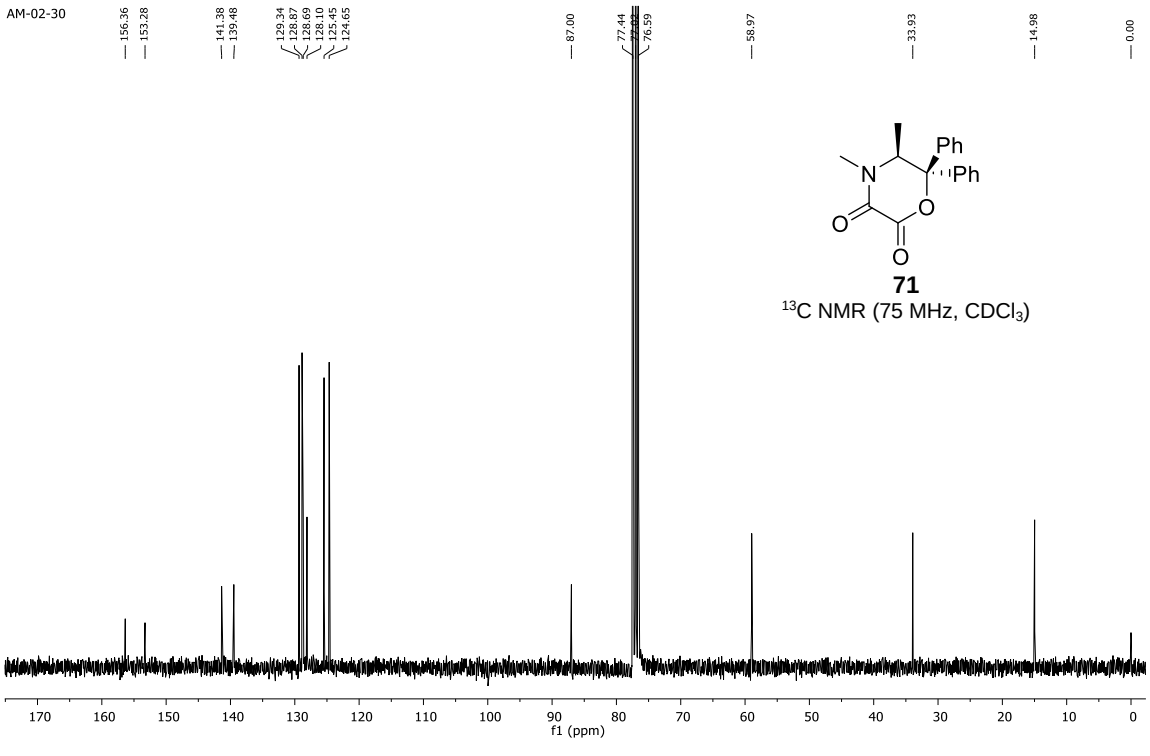

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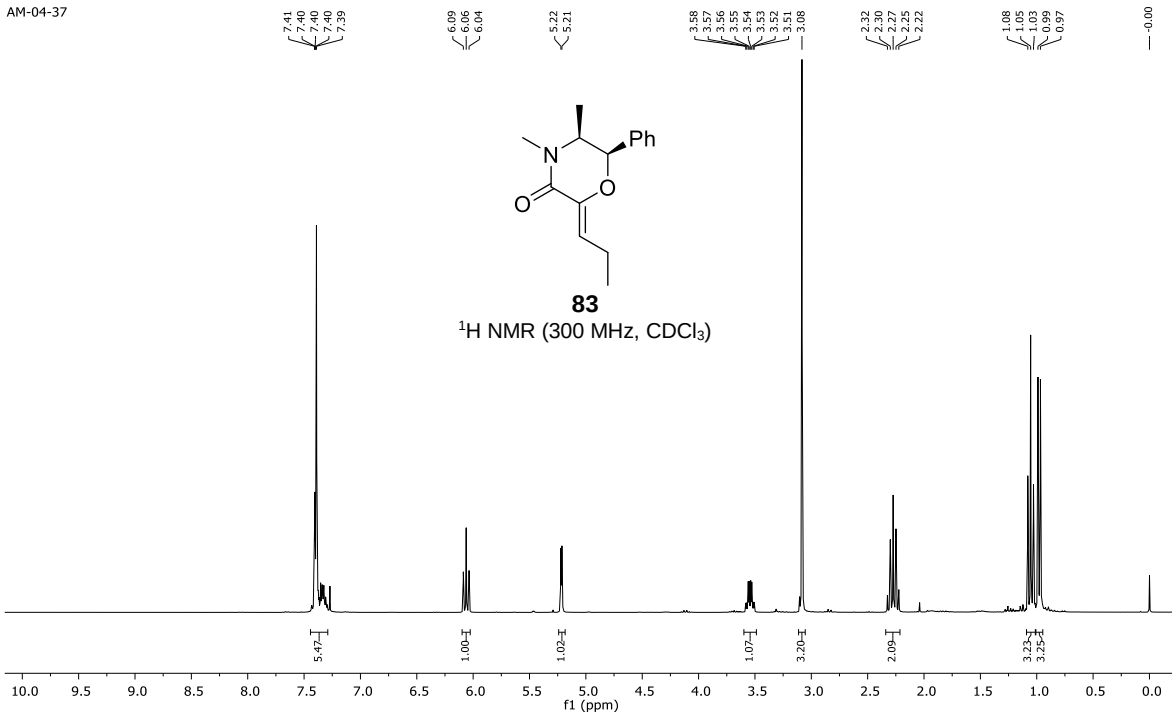

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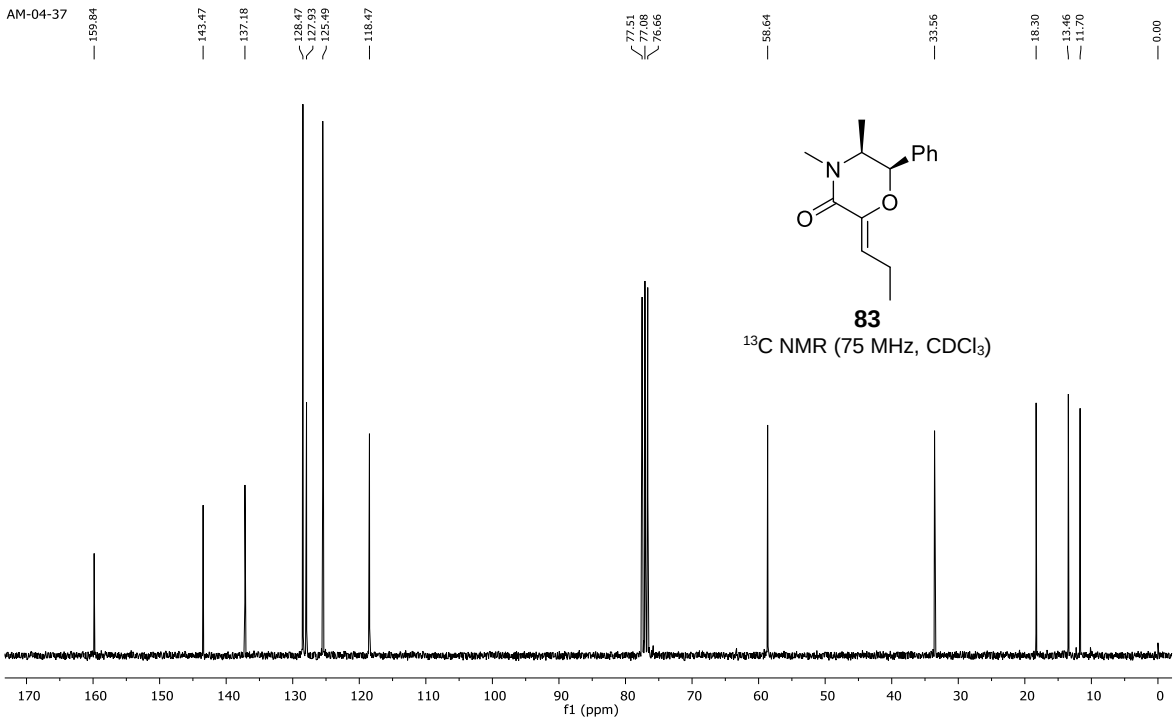

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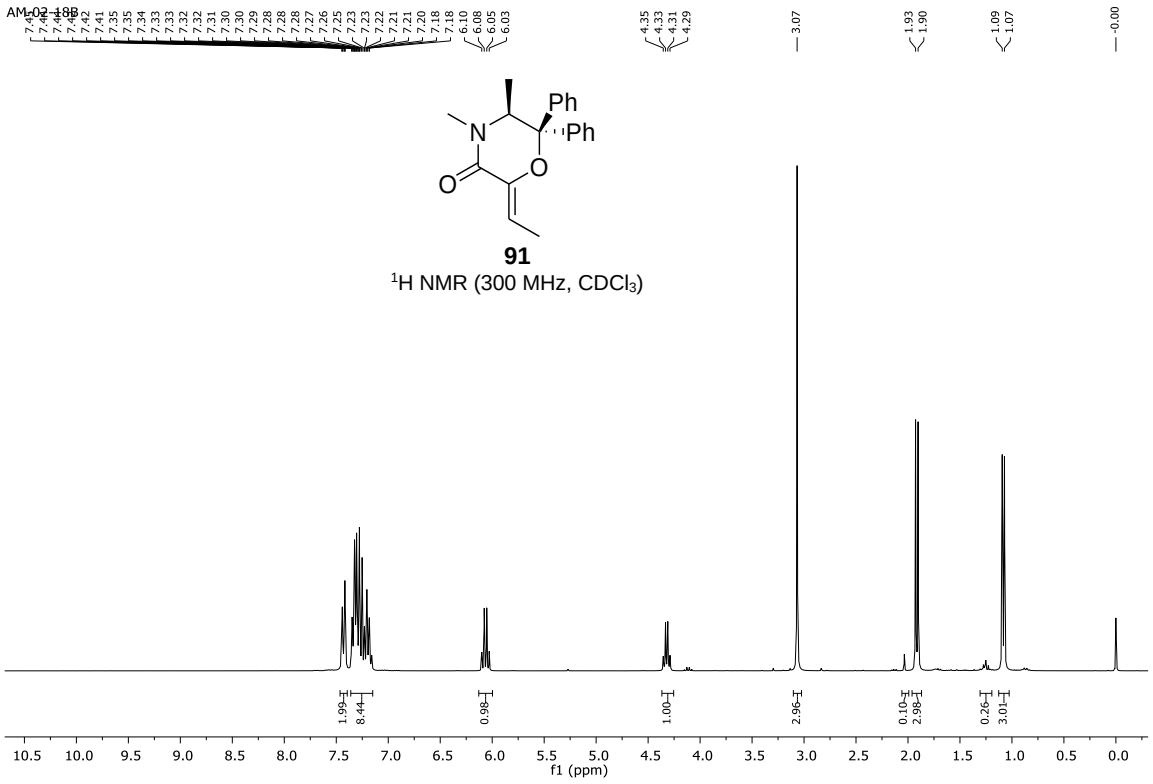

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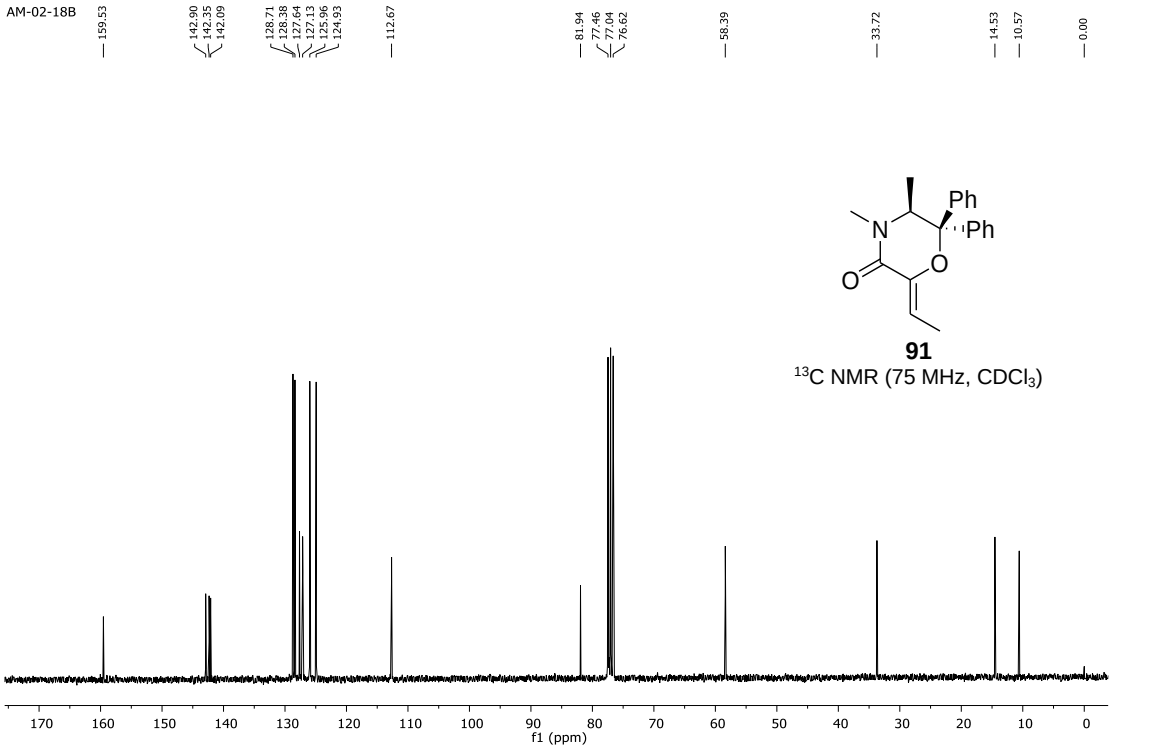

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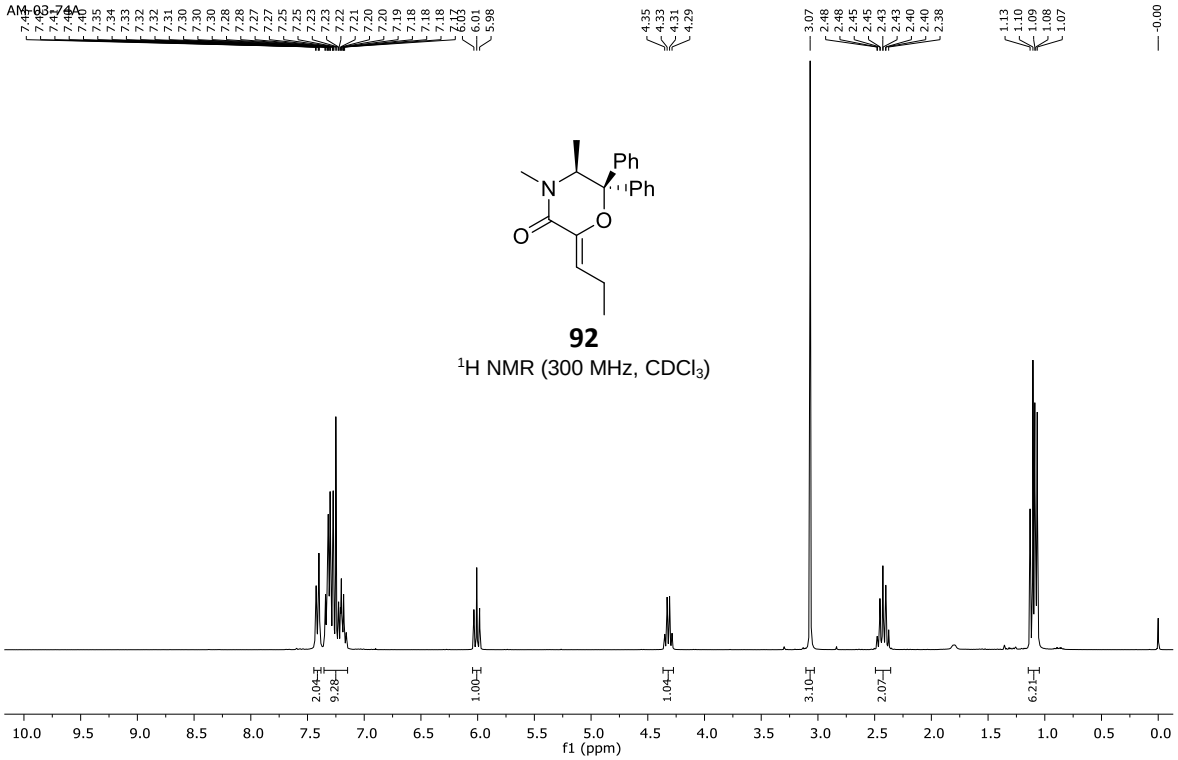

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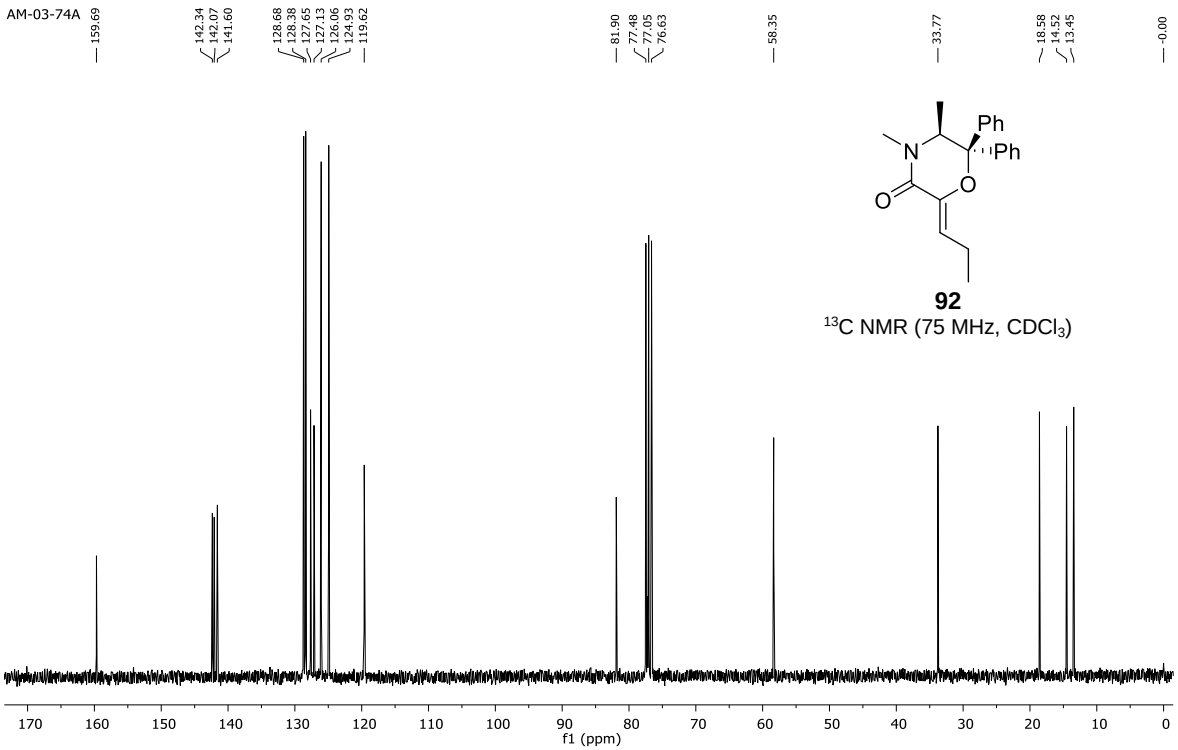

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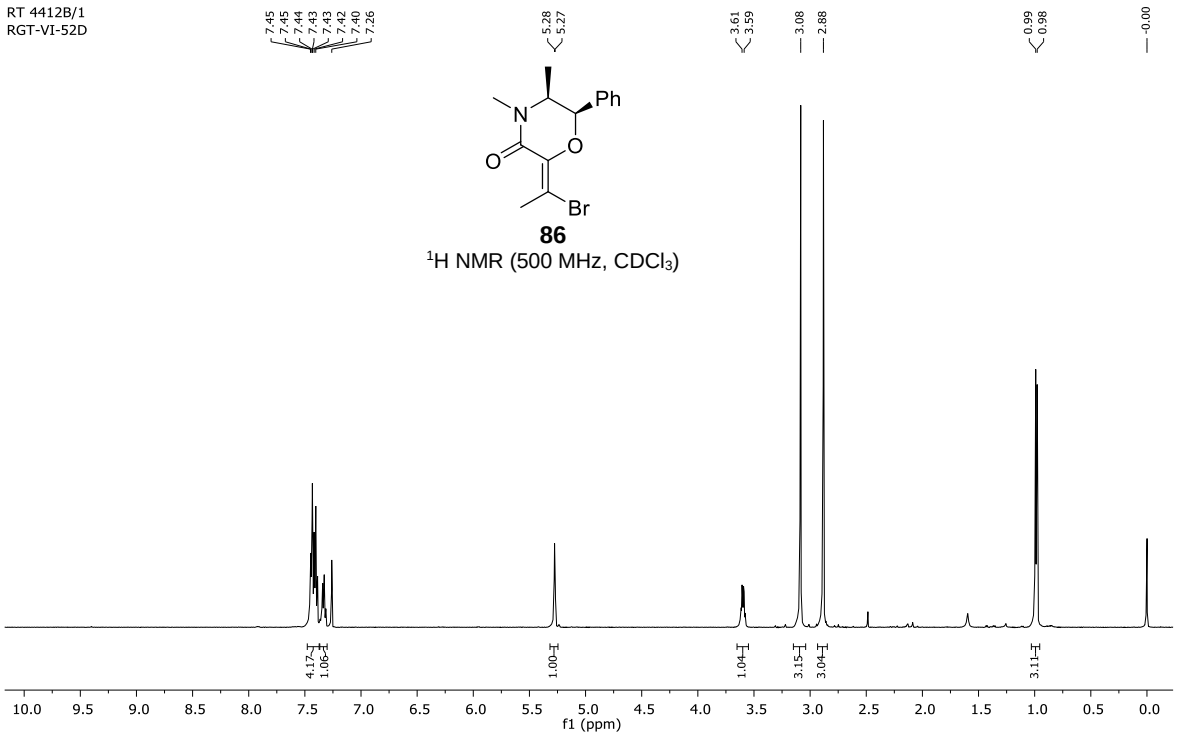

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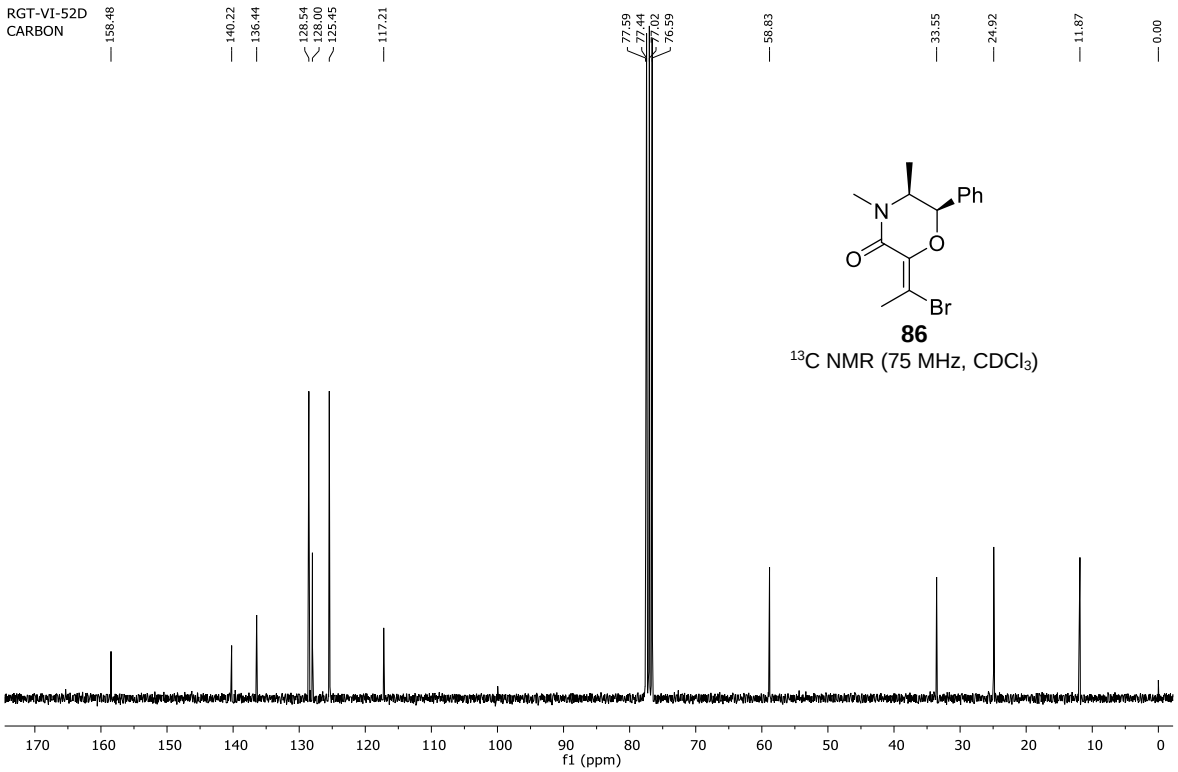

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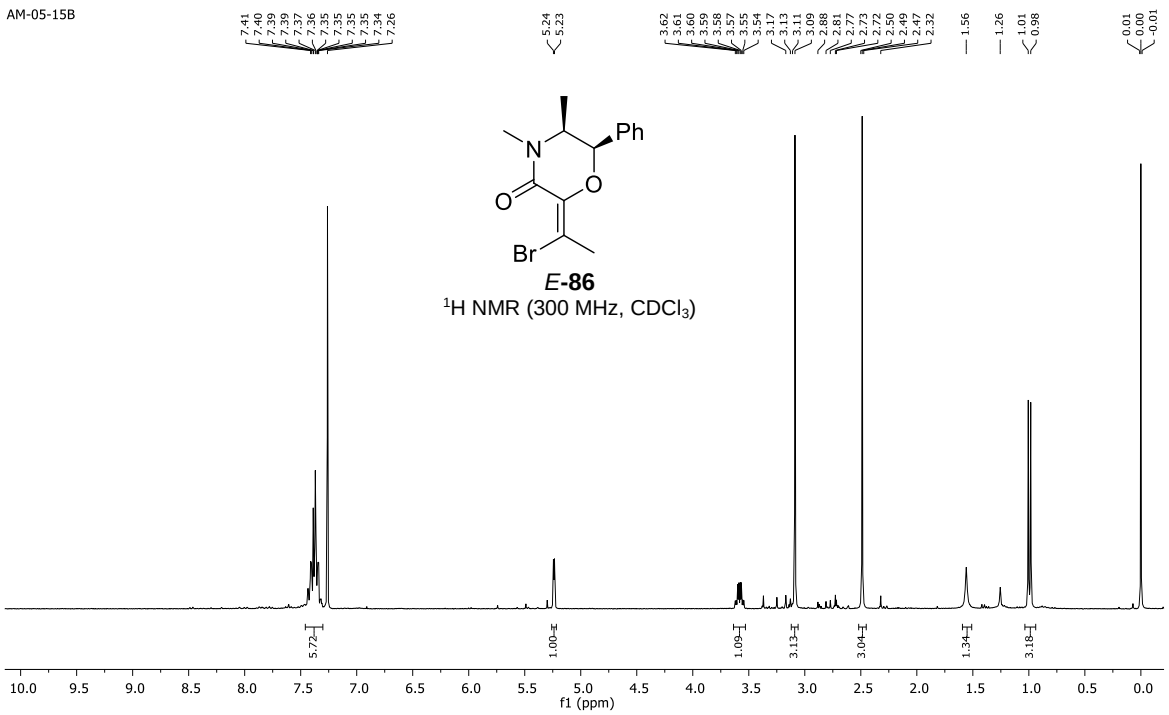

***E*-86**

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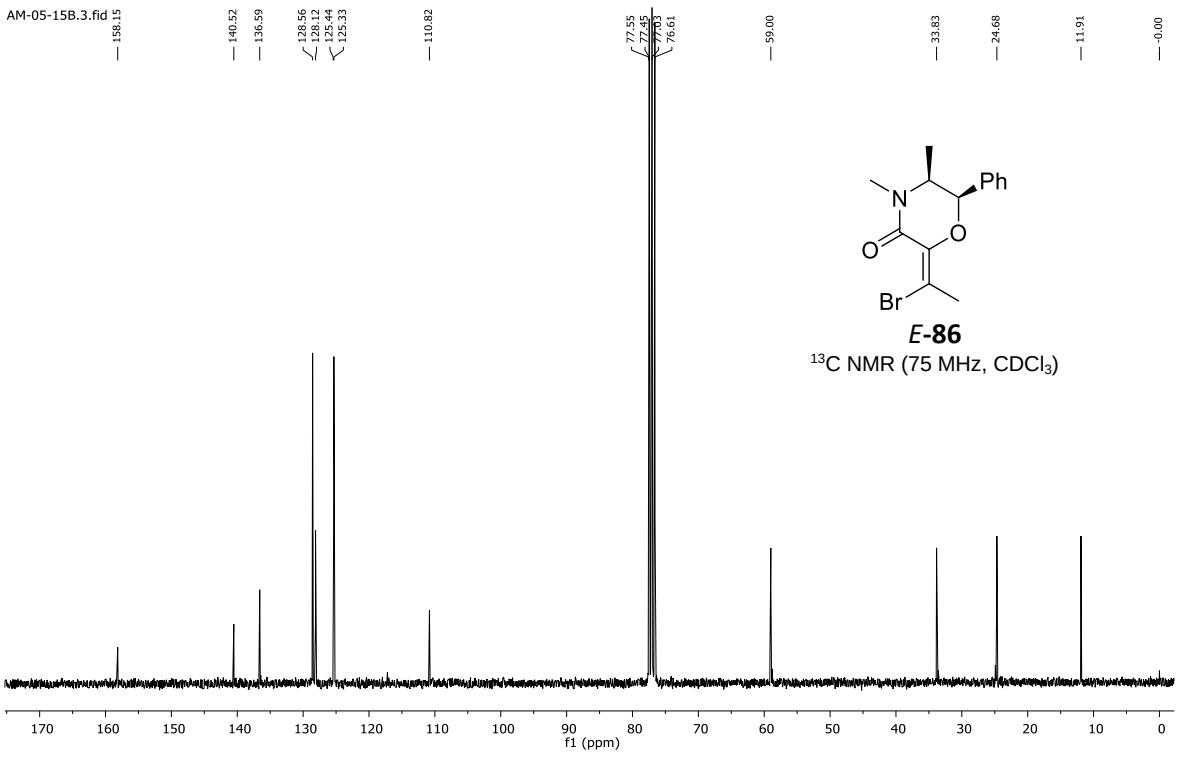

***E*-86**

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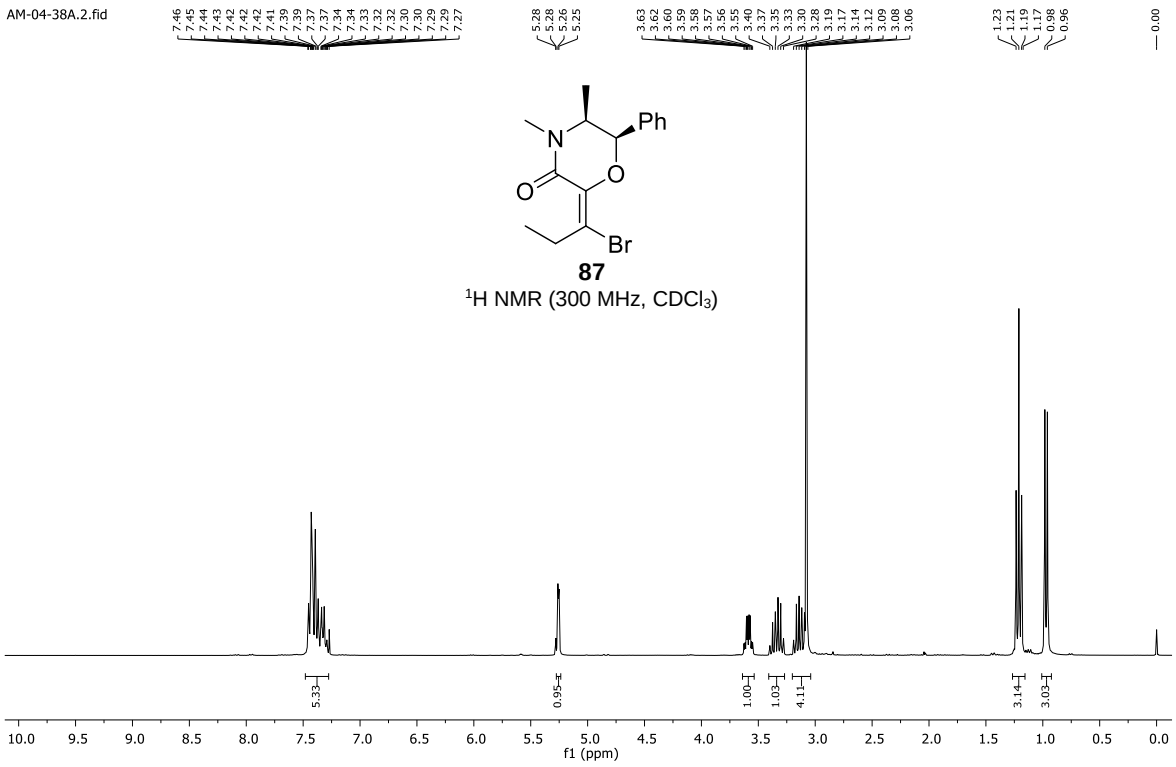
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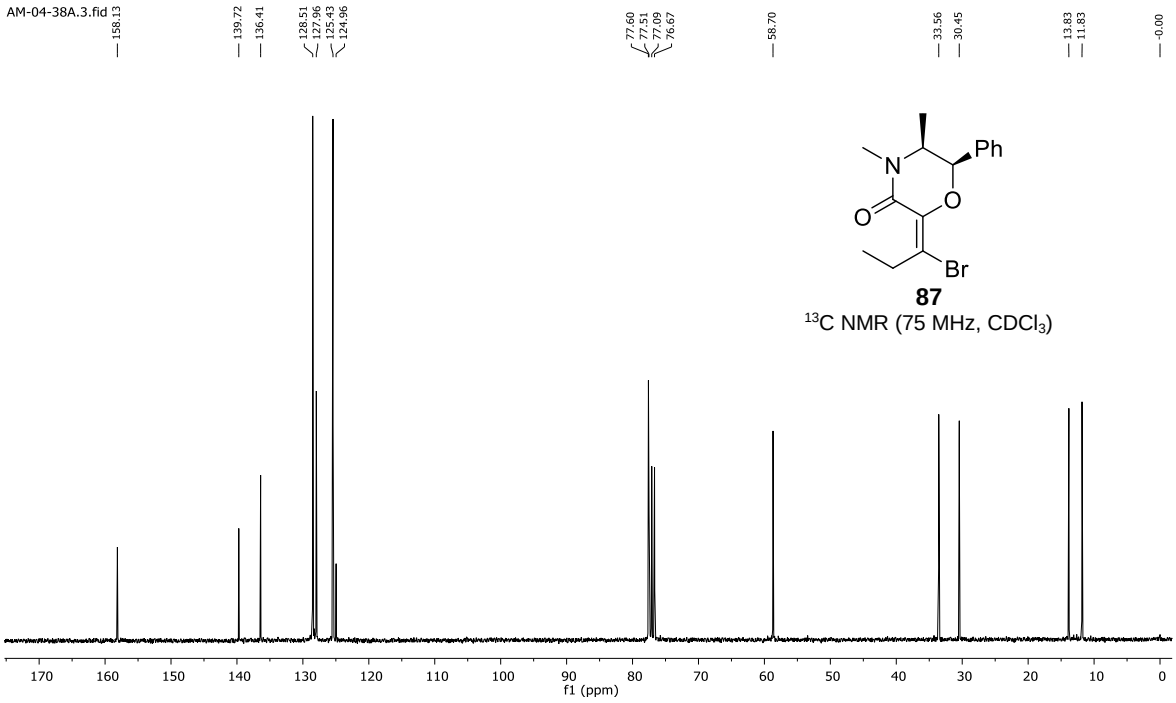
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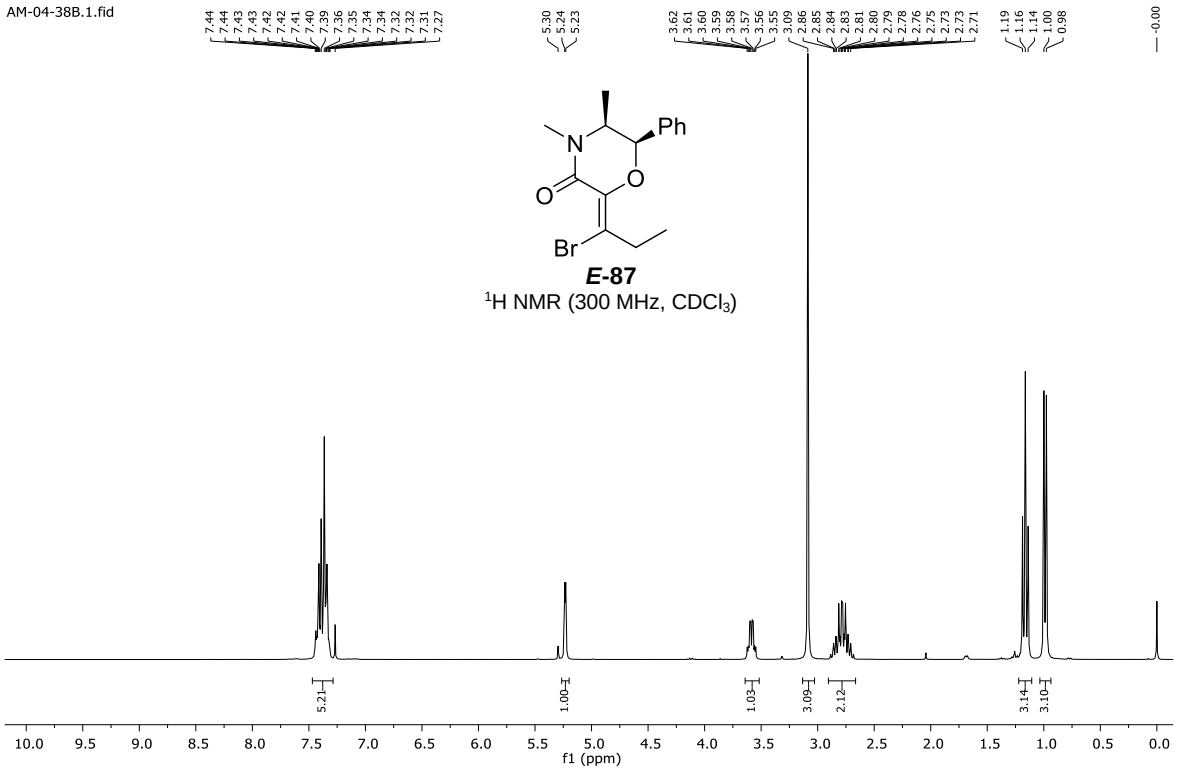
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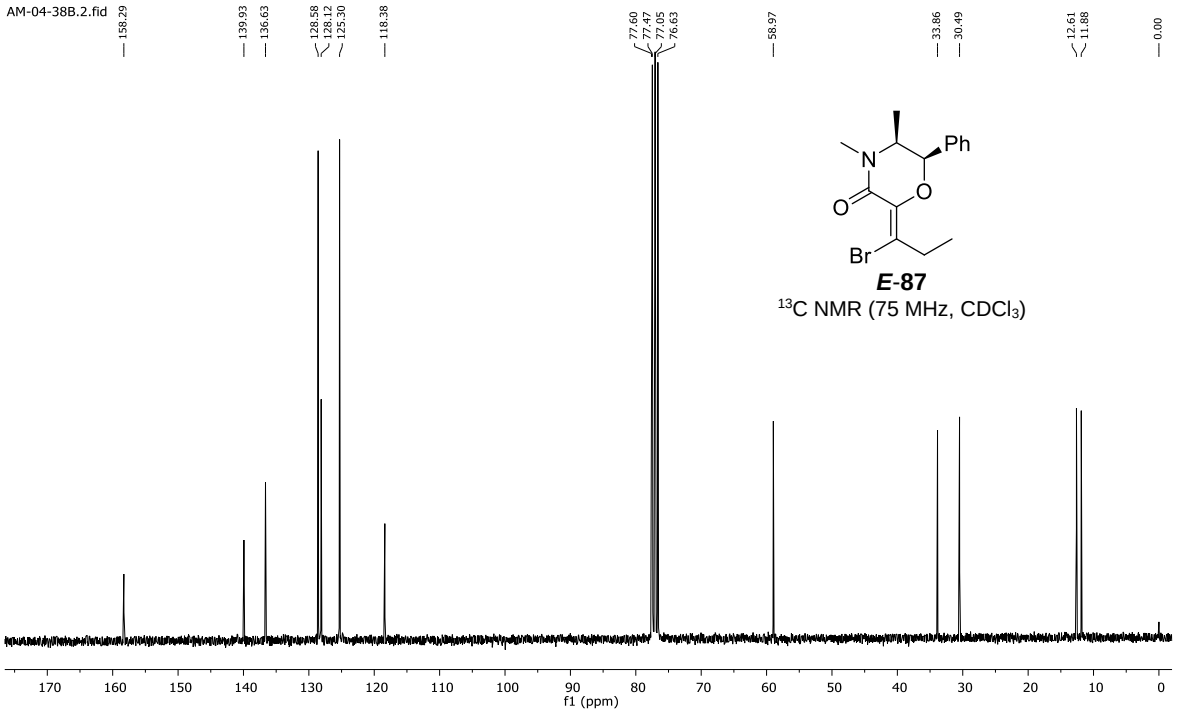
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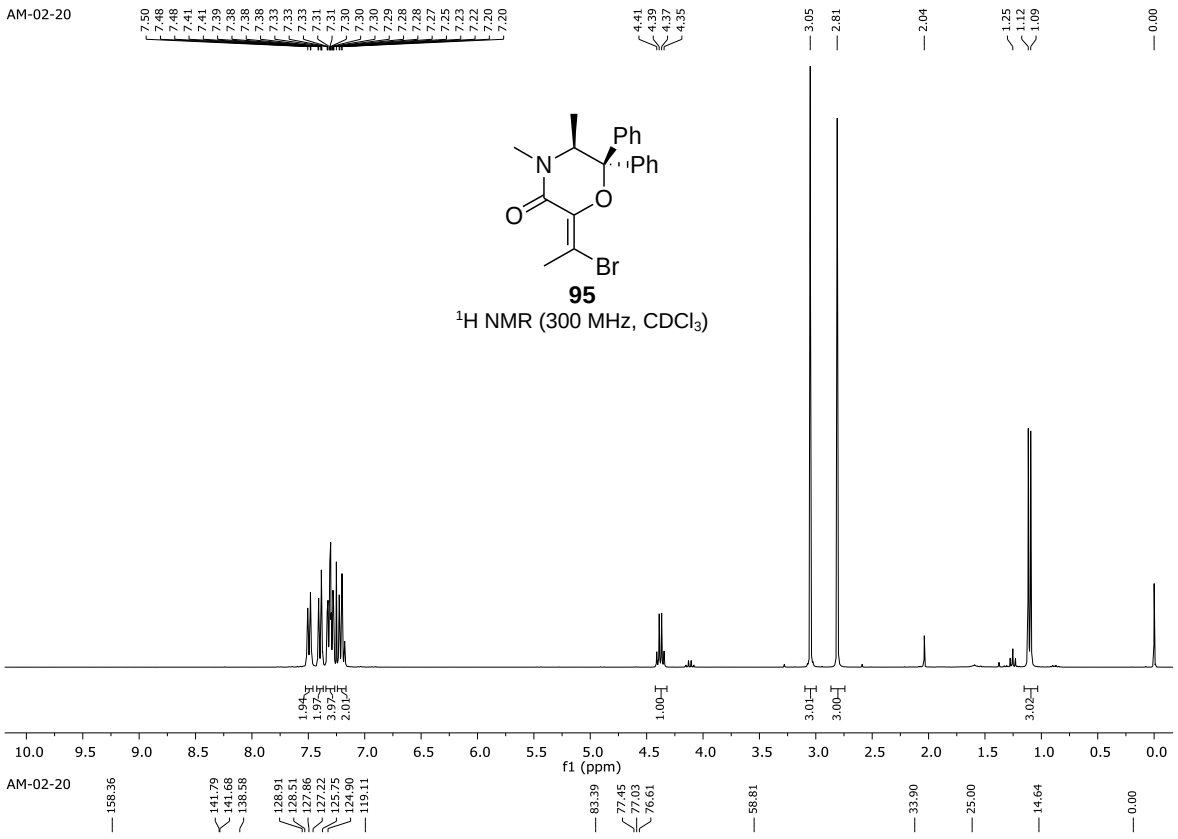
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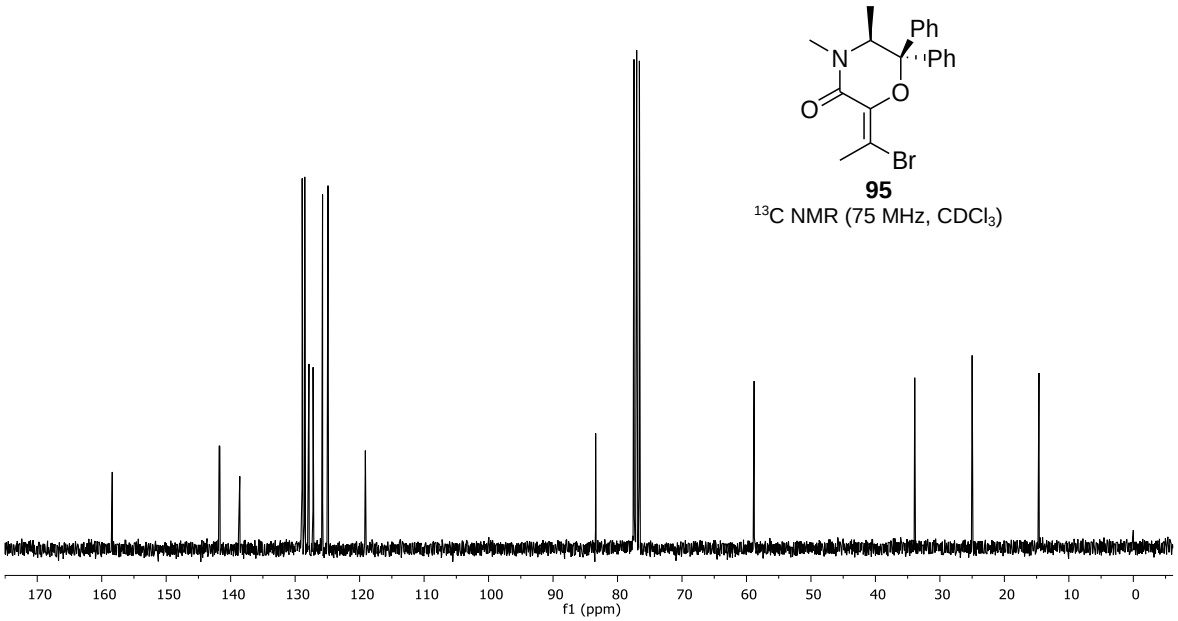
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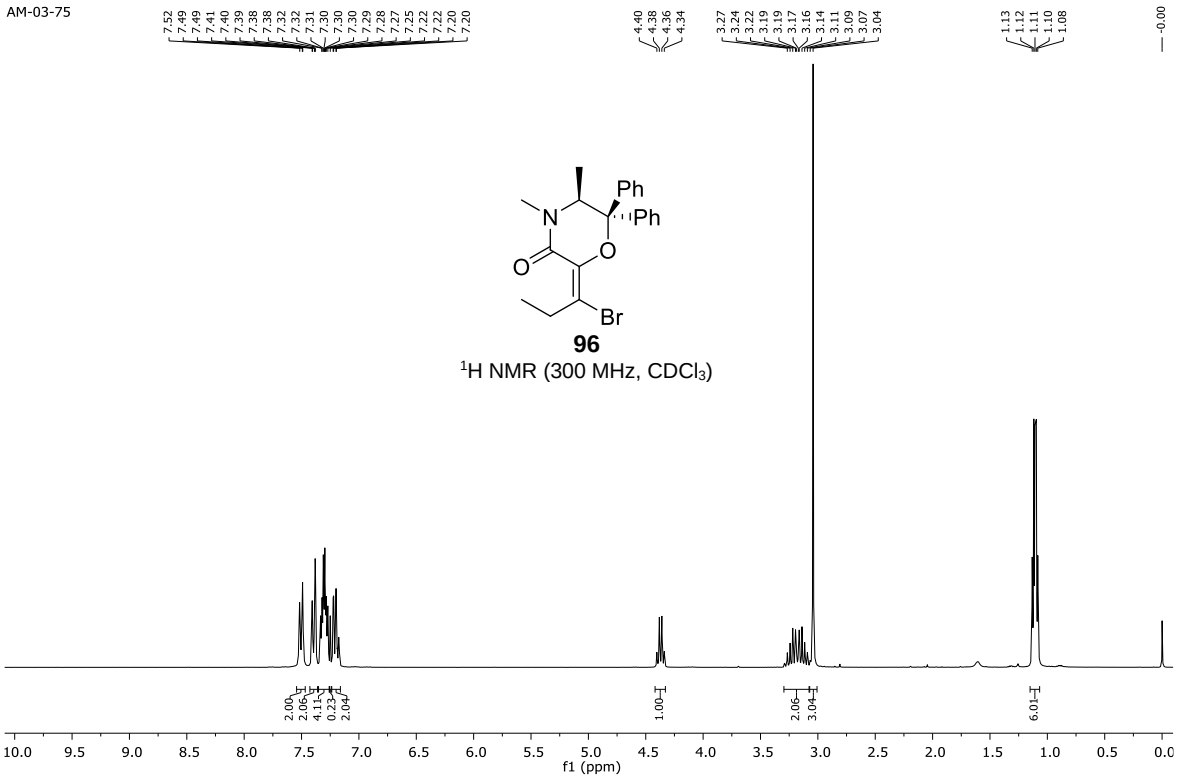
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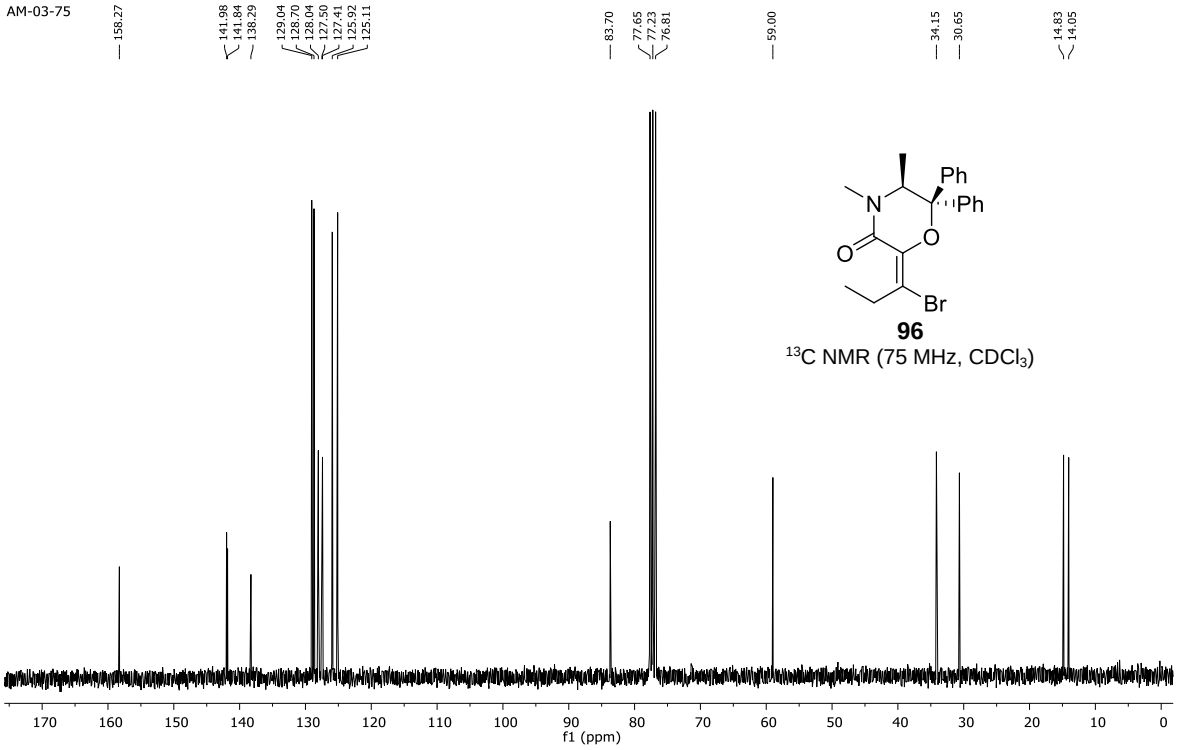
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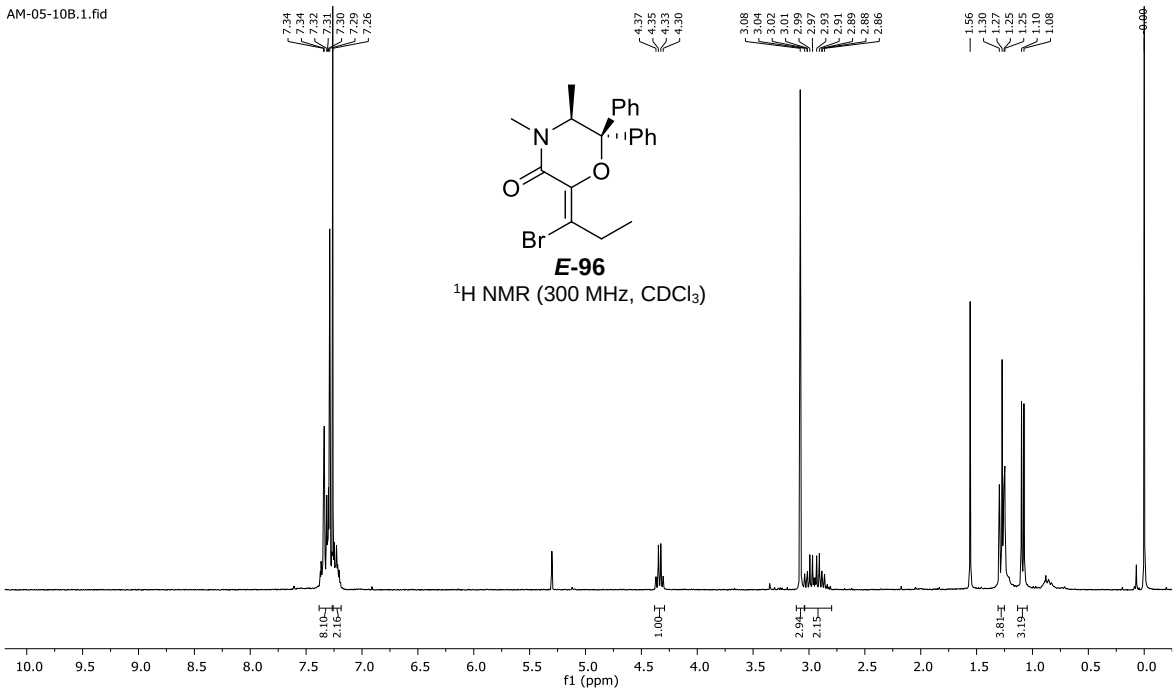

***E*-96**

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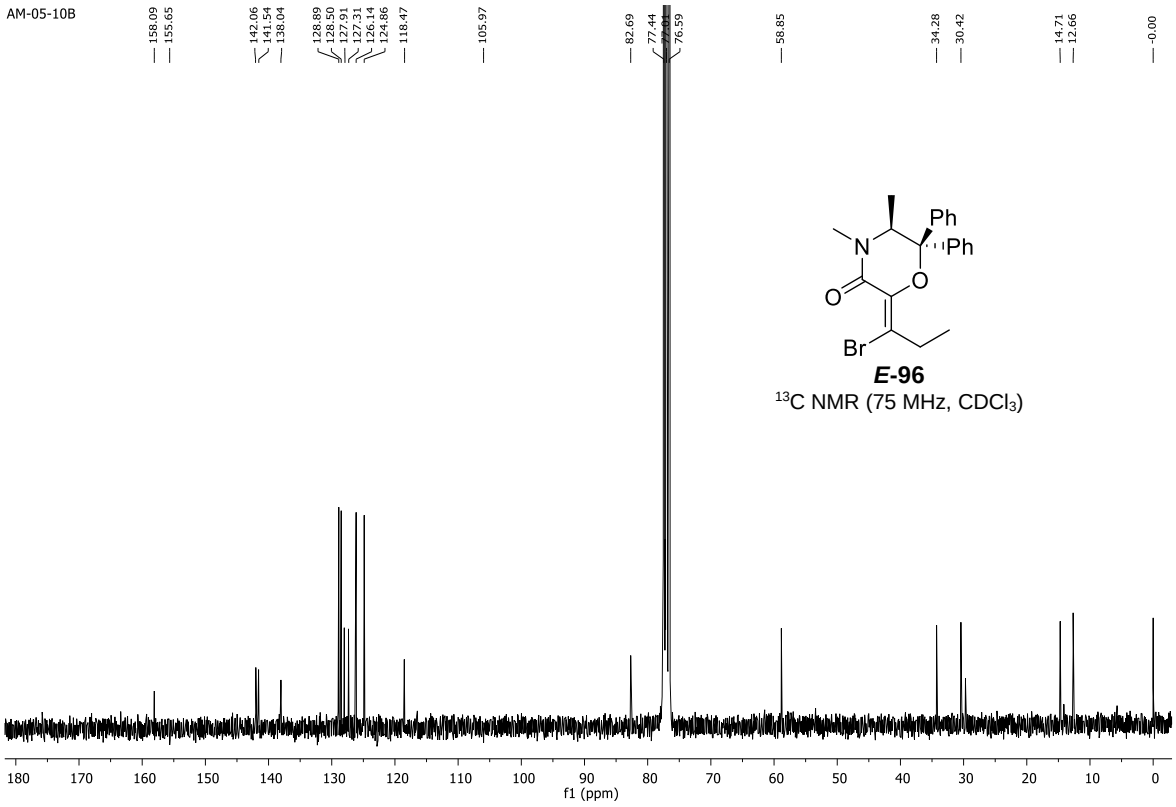

***E*-96**

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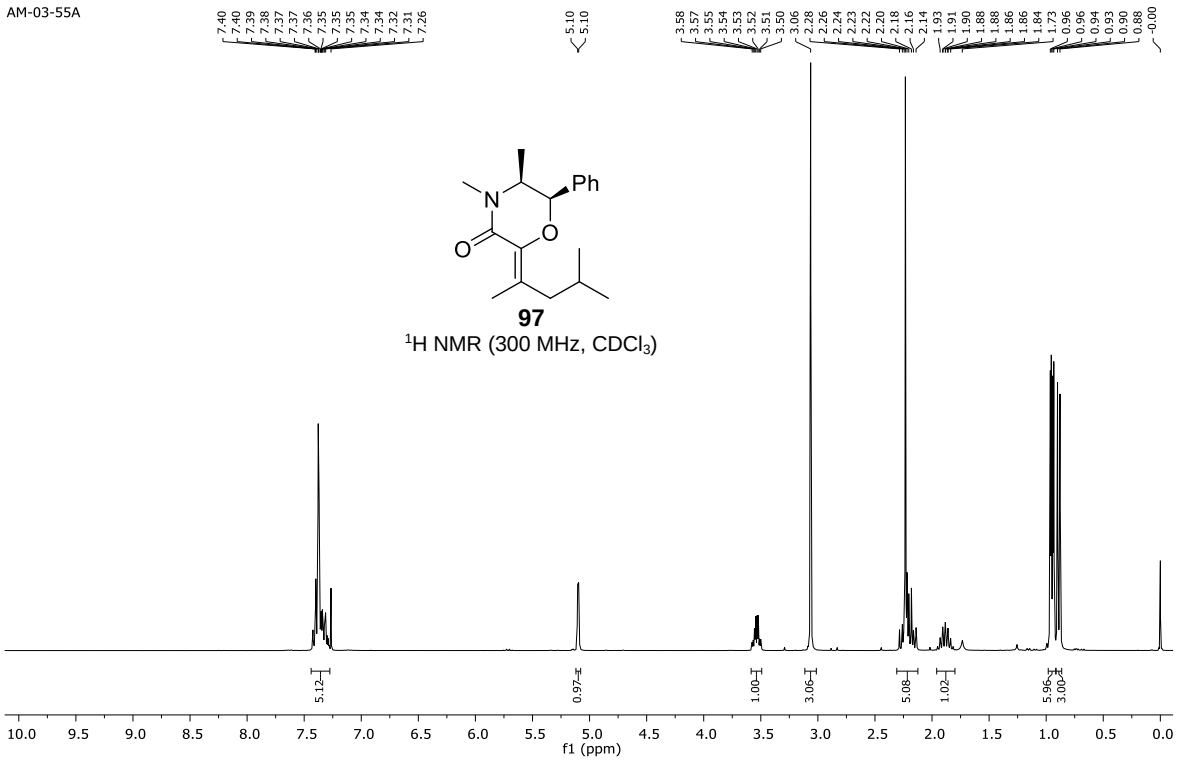

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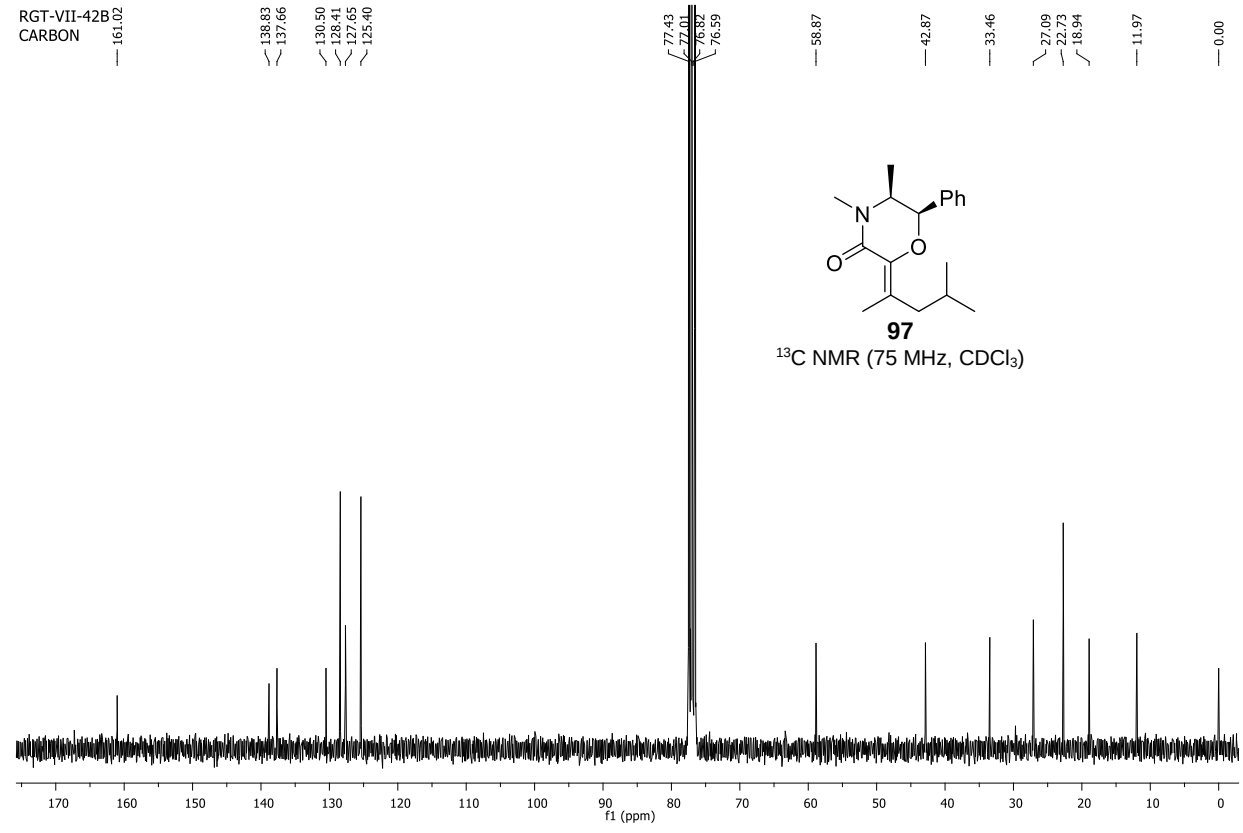
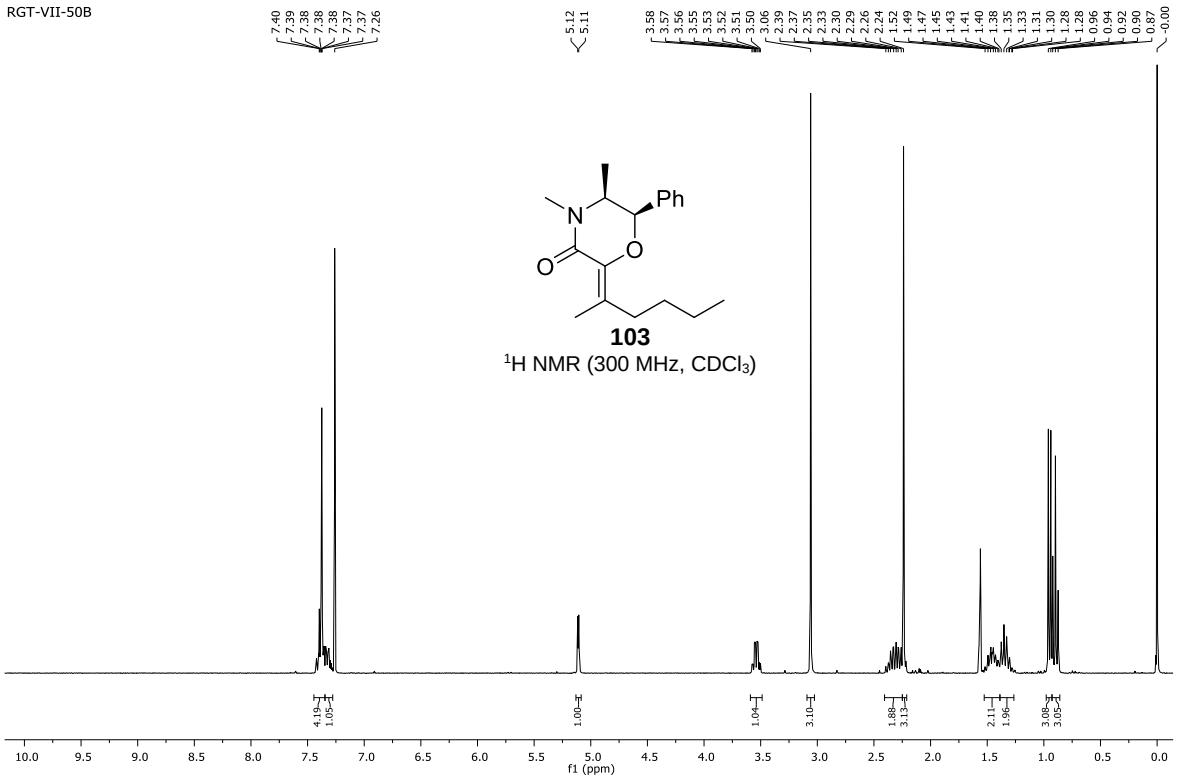


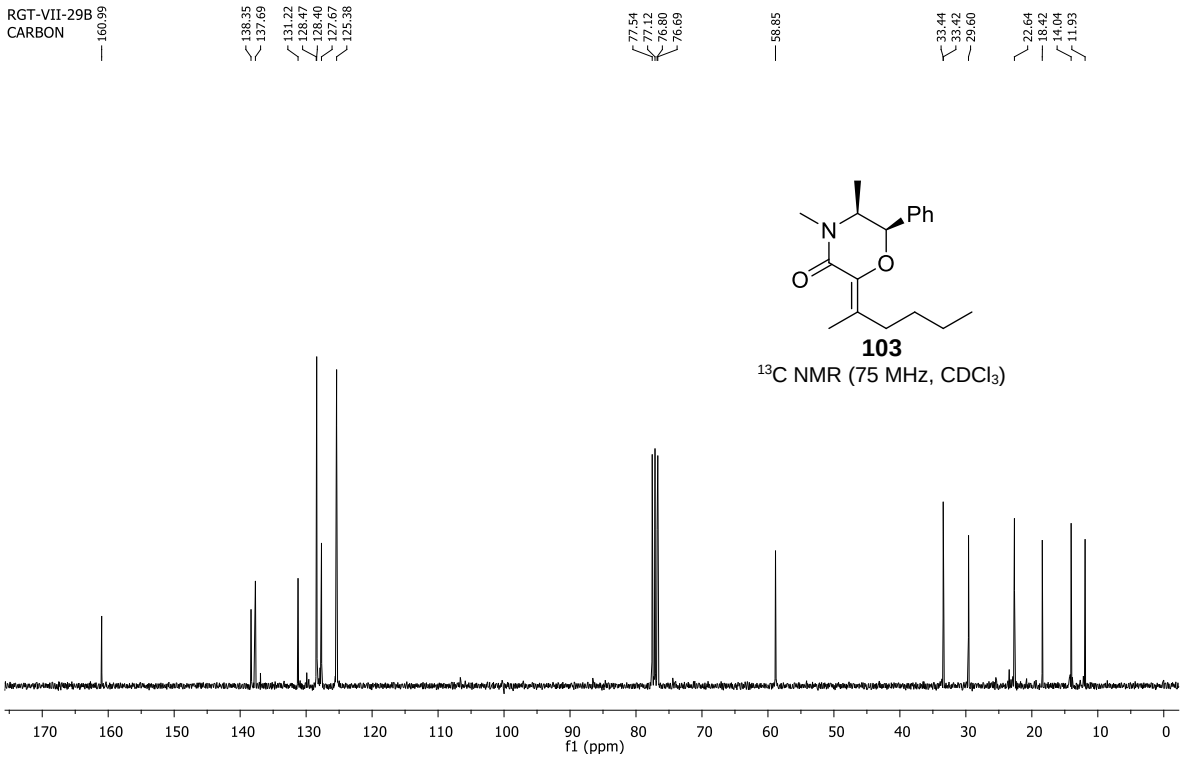
97

^{13}C NMR (75 MHz, $CDCl_3$)



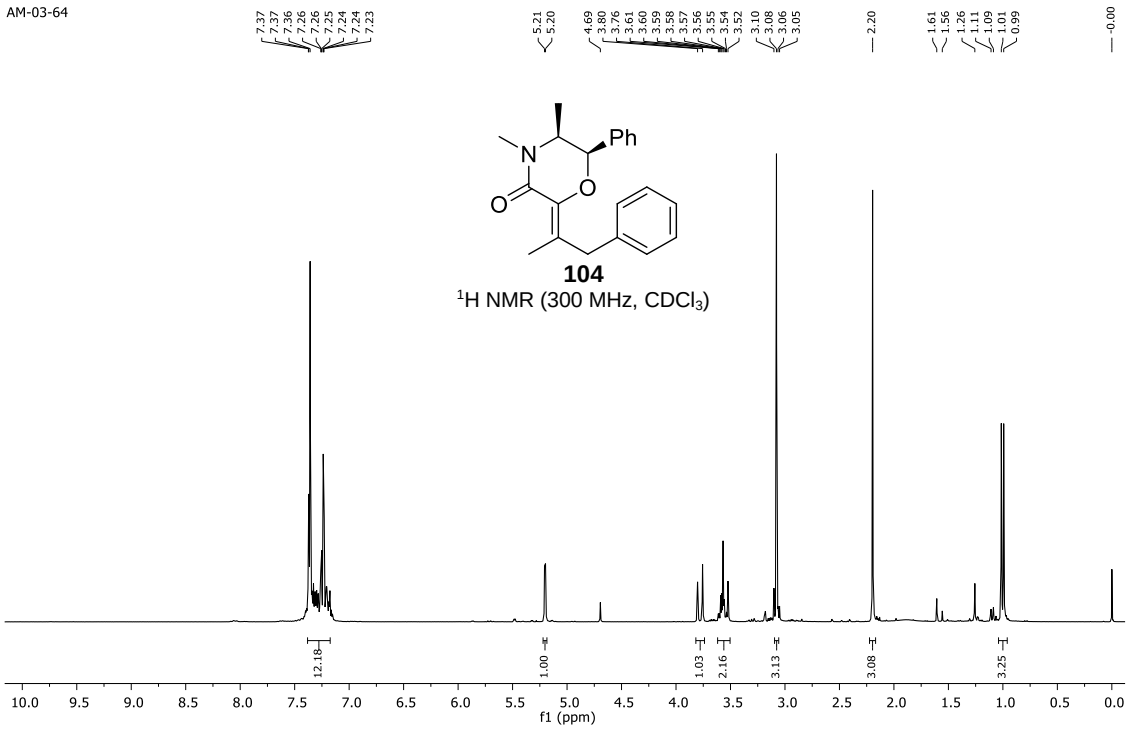
103

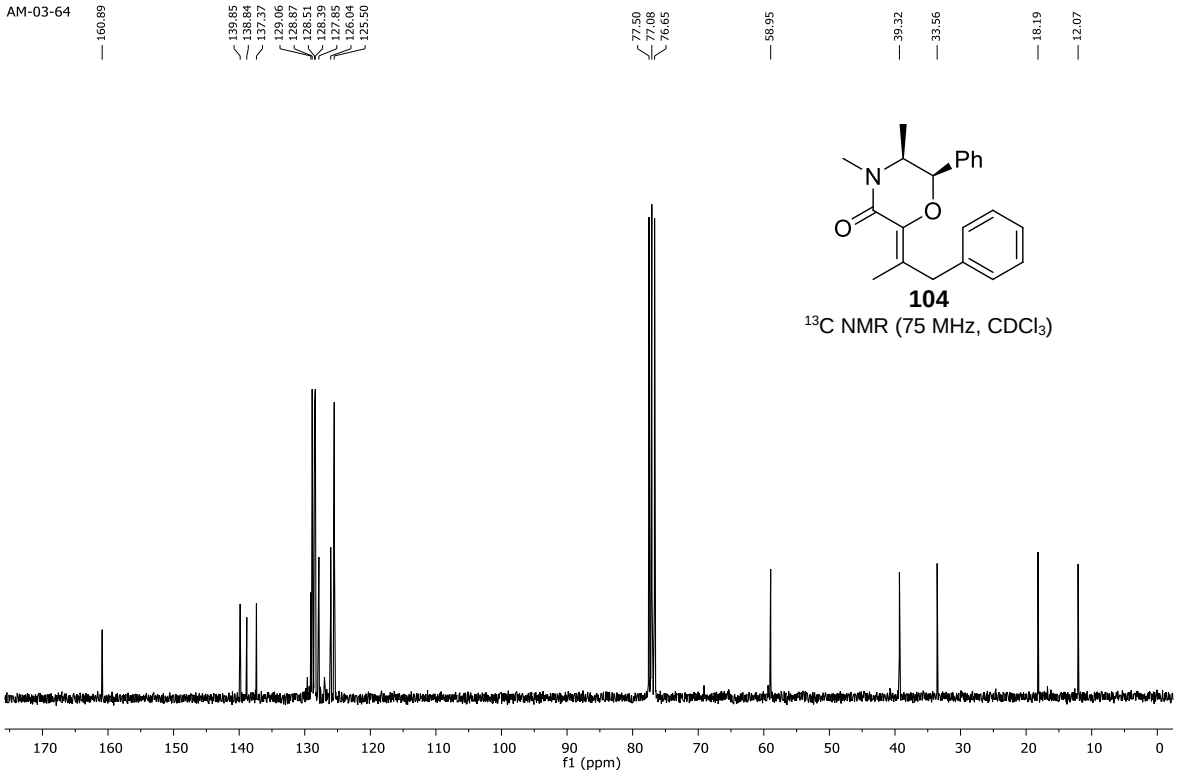
^{1}H NMR (300 MHz, $CDCl_3$)

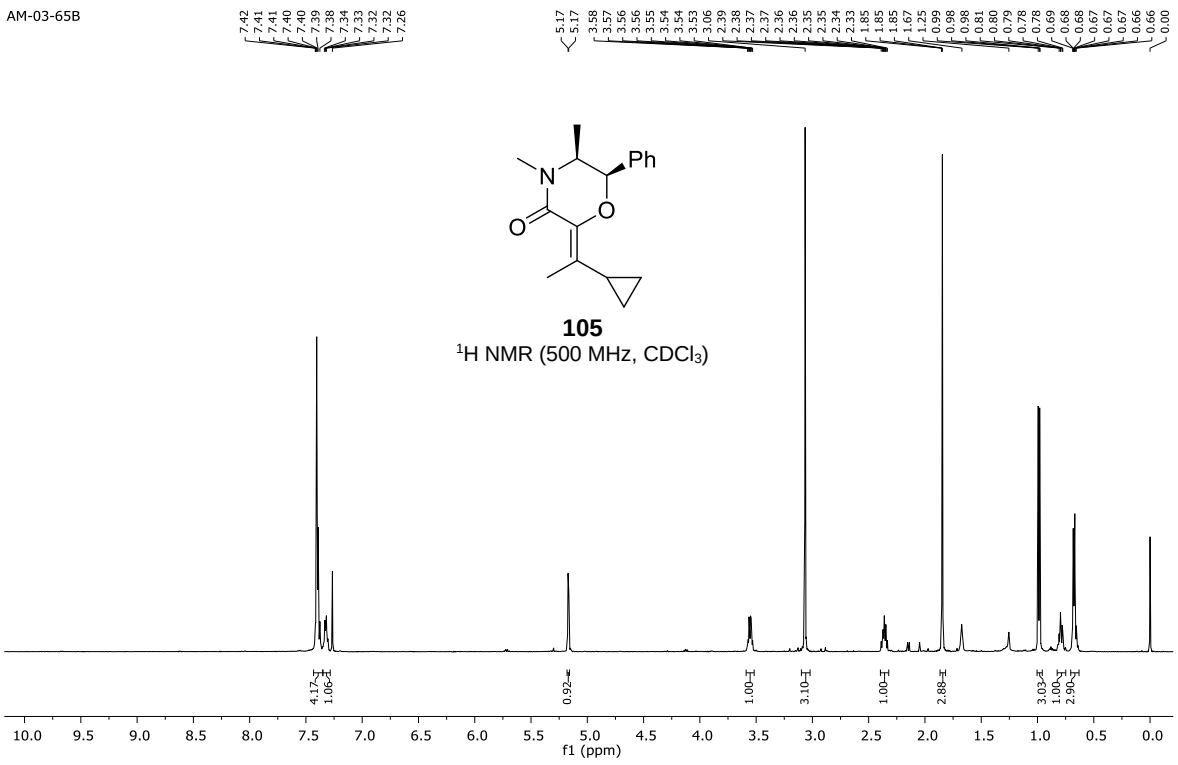


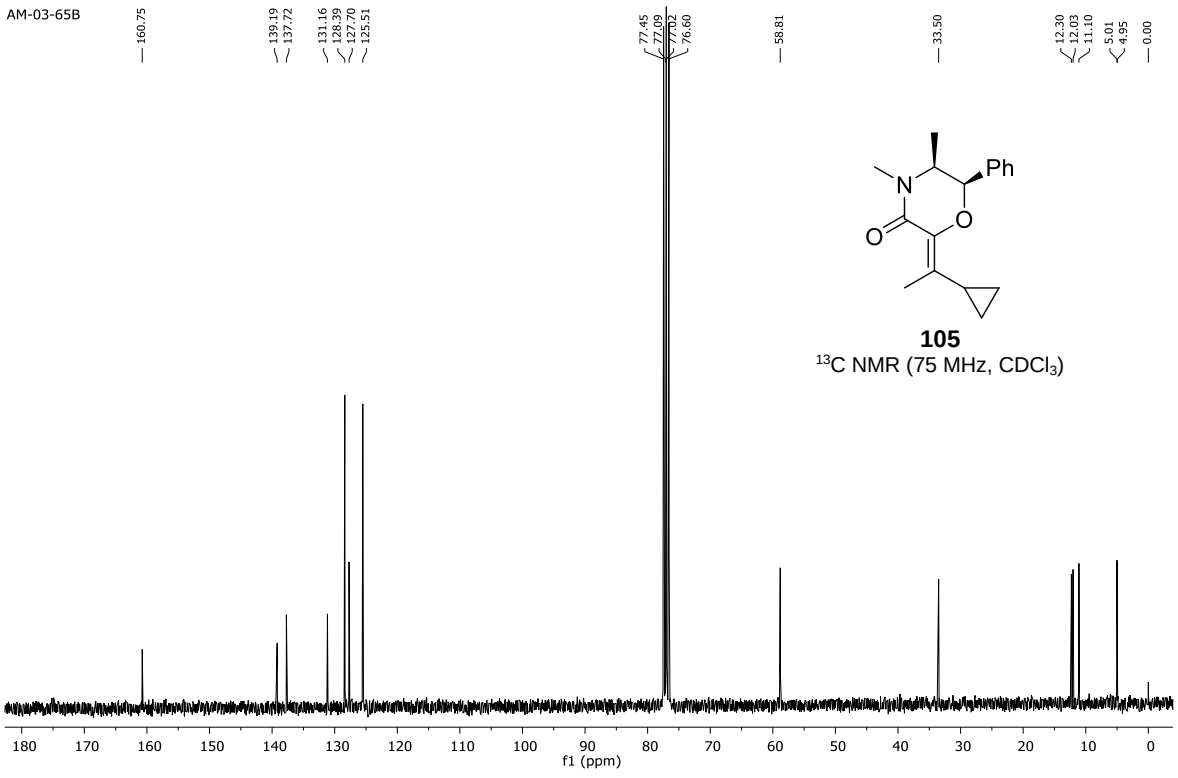
103

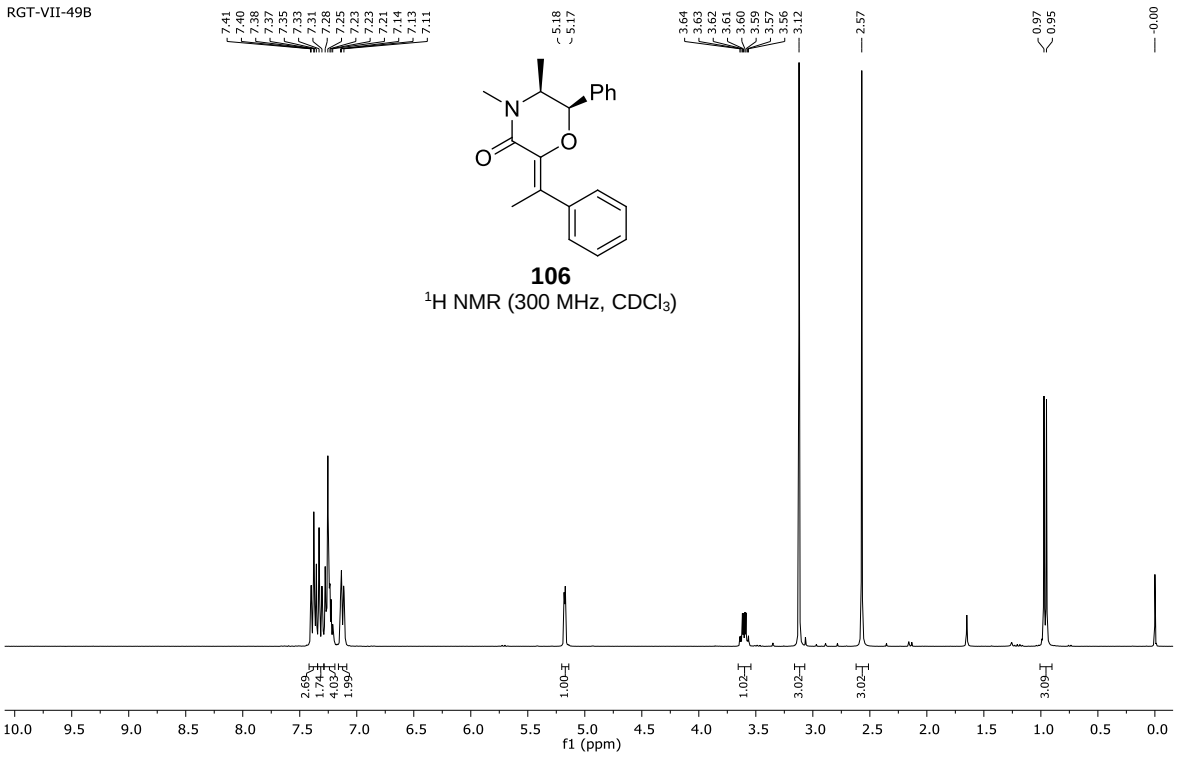
^{13}C NMR (75 MHz, $CDCl_3$)


AM-03-64
7.37
7.37
7.36
7.26
7.26
7.25
7.24
7.24
7.23
5.21
5.20
4.69
3.80
3.76
3.61
3.60
3.59
3.58
3.57
3.56
3.55
3.54
3.52
3.10
3.08
3.06
3.05
2.20
1.61
1.56
1.26
1.11
1.09
1.01
0.99
-0.00
Ph
N
O
O
104
1H NMR (300 MHz, CDCl3)
12.18
1.00
1.03
2.16
3.13
3.08
3.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AM-03-64
160.89
139.85
138.84
137.37
129.06
128.87
128.51
128.39
127.85
126.04
125.50
77.50
77.08
76.65
58.95
39.32
33.56
18.19
12.07
Ph
N
O
O
104
13C NMR (75 MHz, CDCl3)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

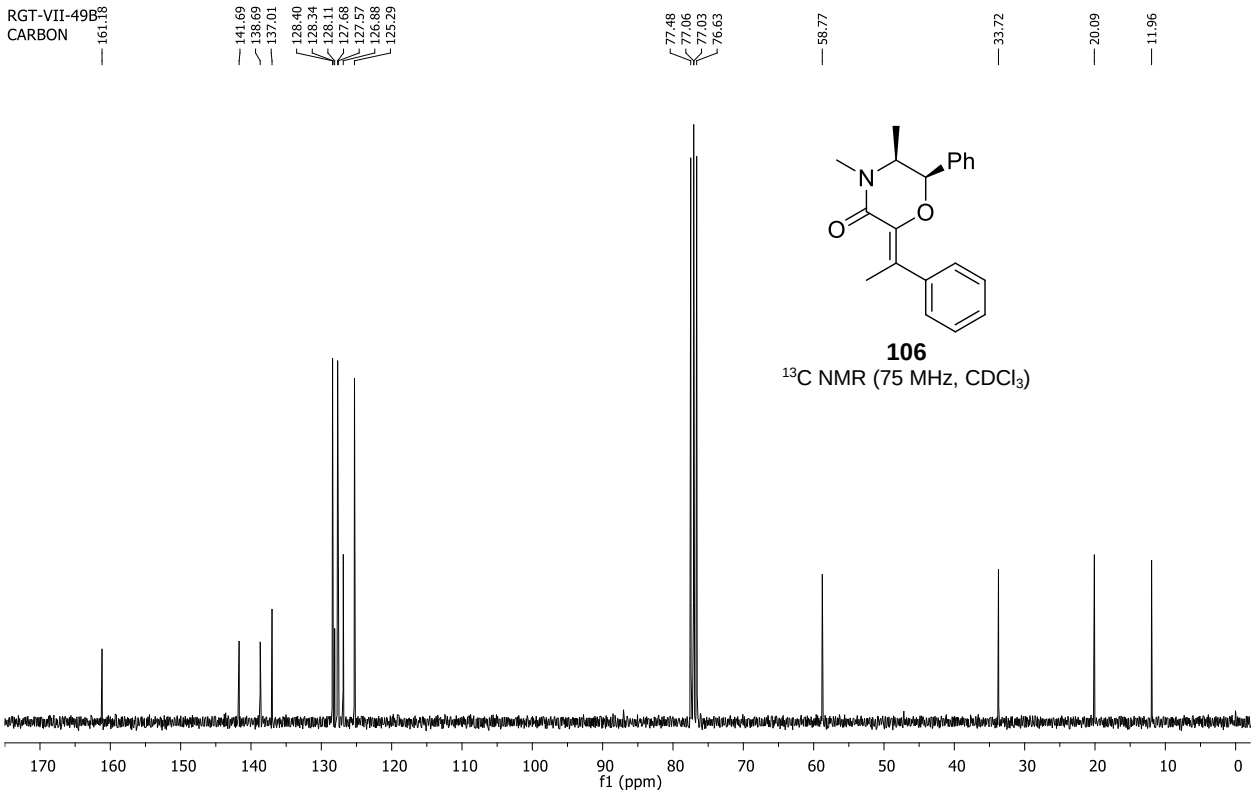

AM-03-65B
Ph
N
O
O
105
1H NMR (500 MHz, CDCl3)
f1 (ppm)


AM-03-65B
Ph
N
O
O
105
13C NMR (75 MHz, CDCl3)
f1 (ppm)



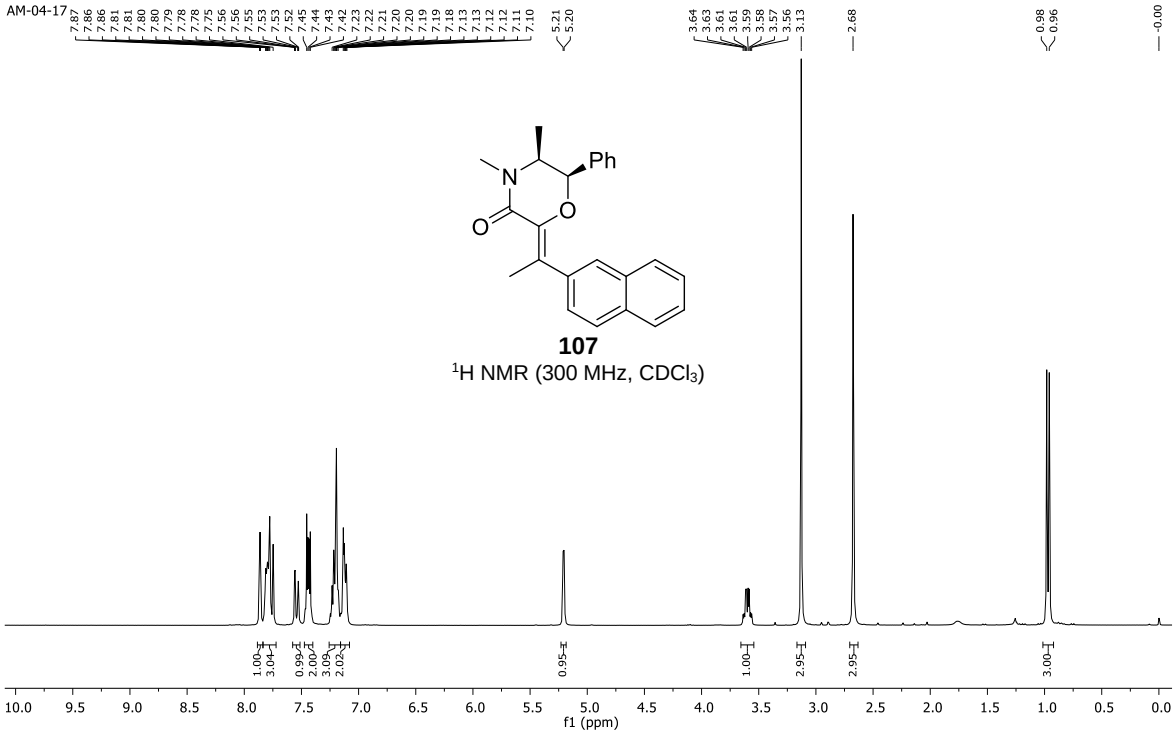
106

^{1}H NMR (300 MHz, $CDCl_3$)



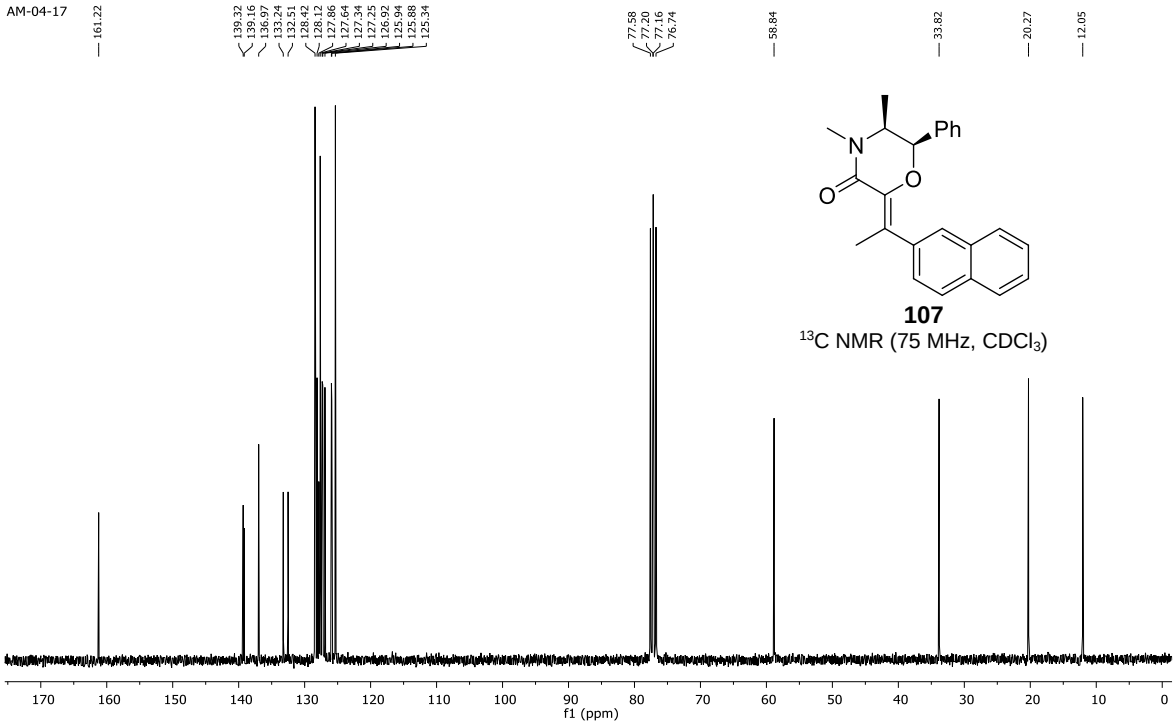
106

^{13}C NMR (75 MHz, $CDCl_3$)



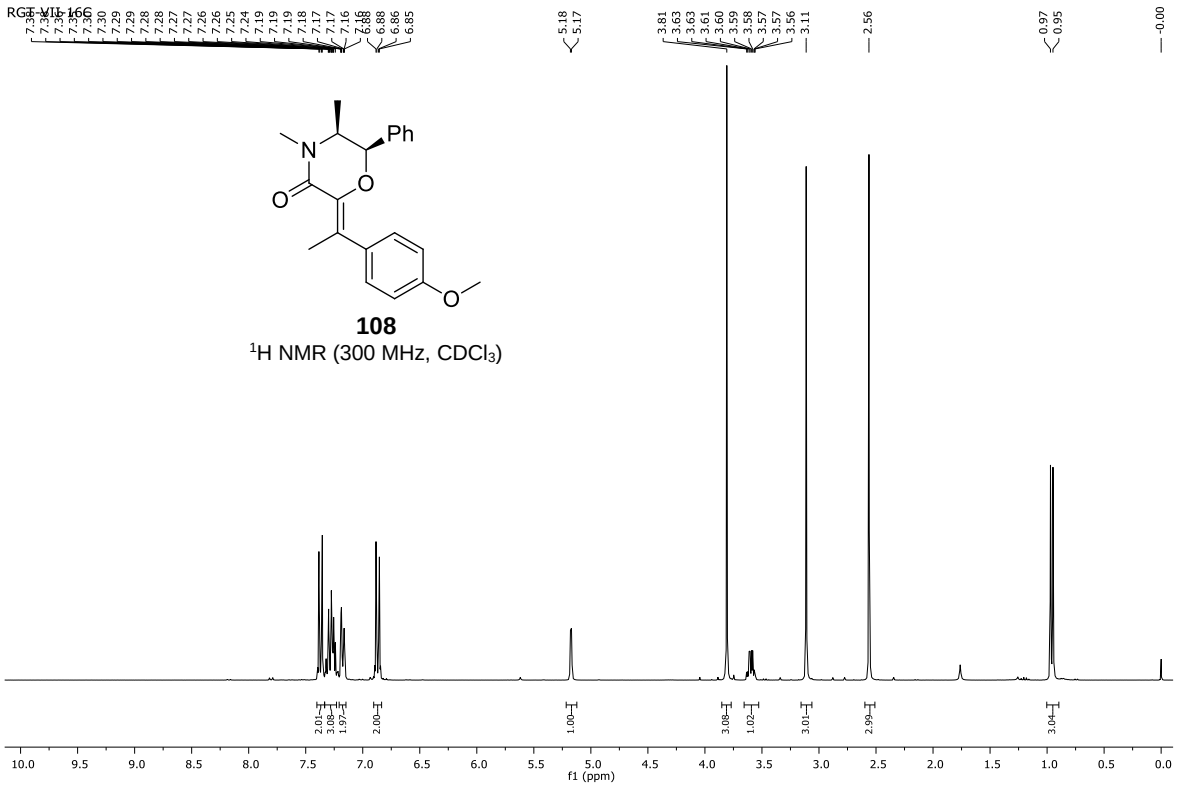
107

^{1}H NMR (300 MHz, $CDCl_3$)



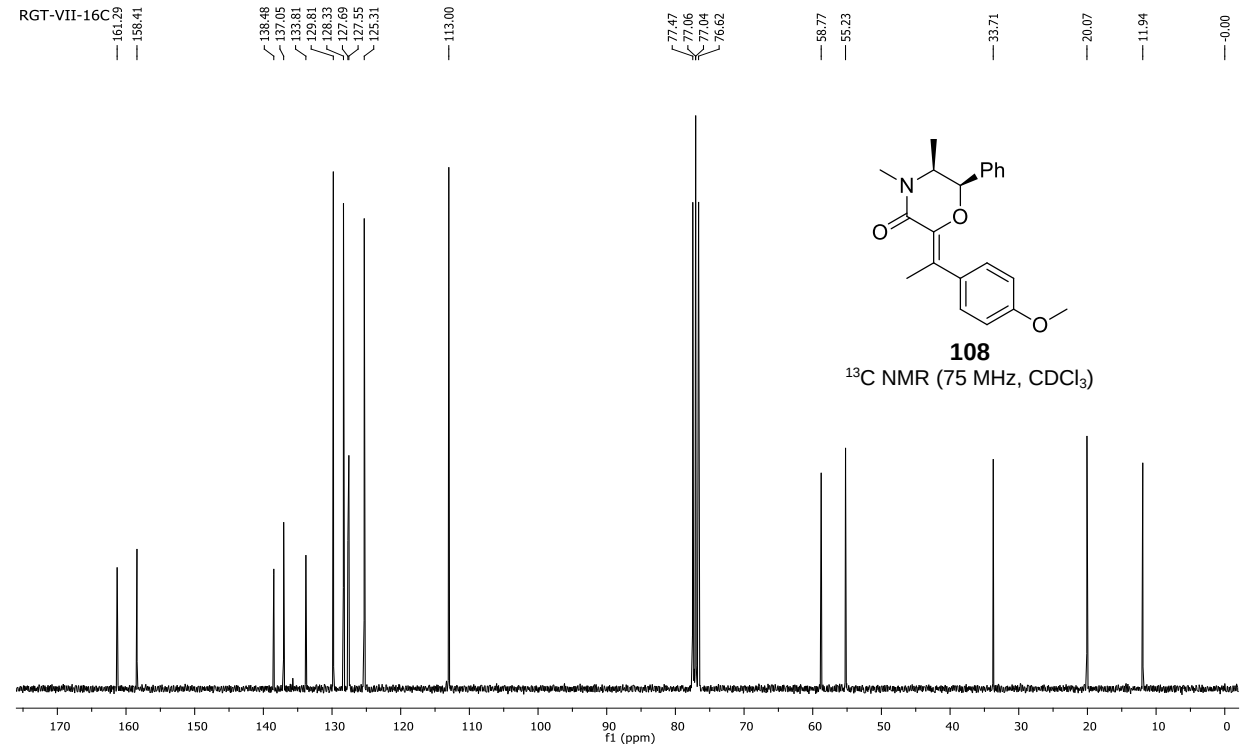
107

^{13}C NMR (75 MHz, $CDCl_3$)



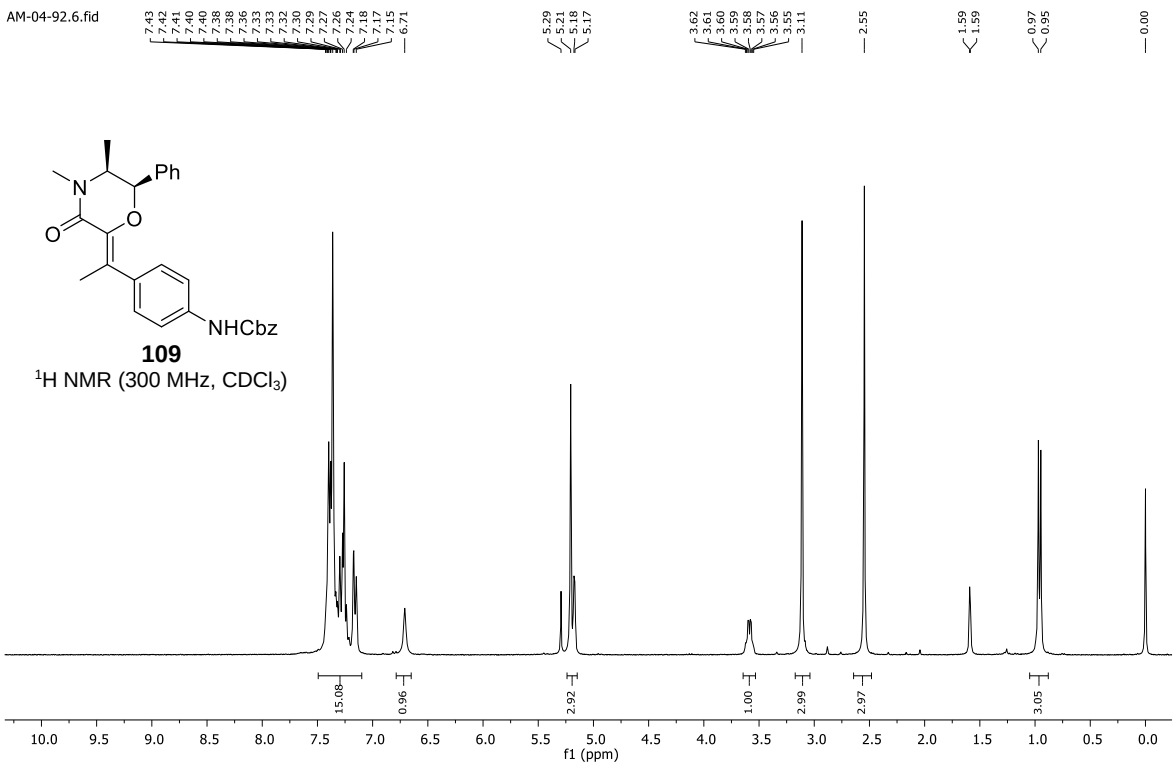
108

^{1}H NMR (300 MHz, $CDCl_3$)



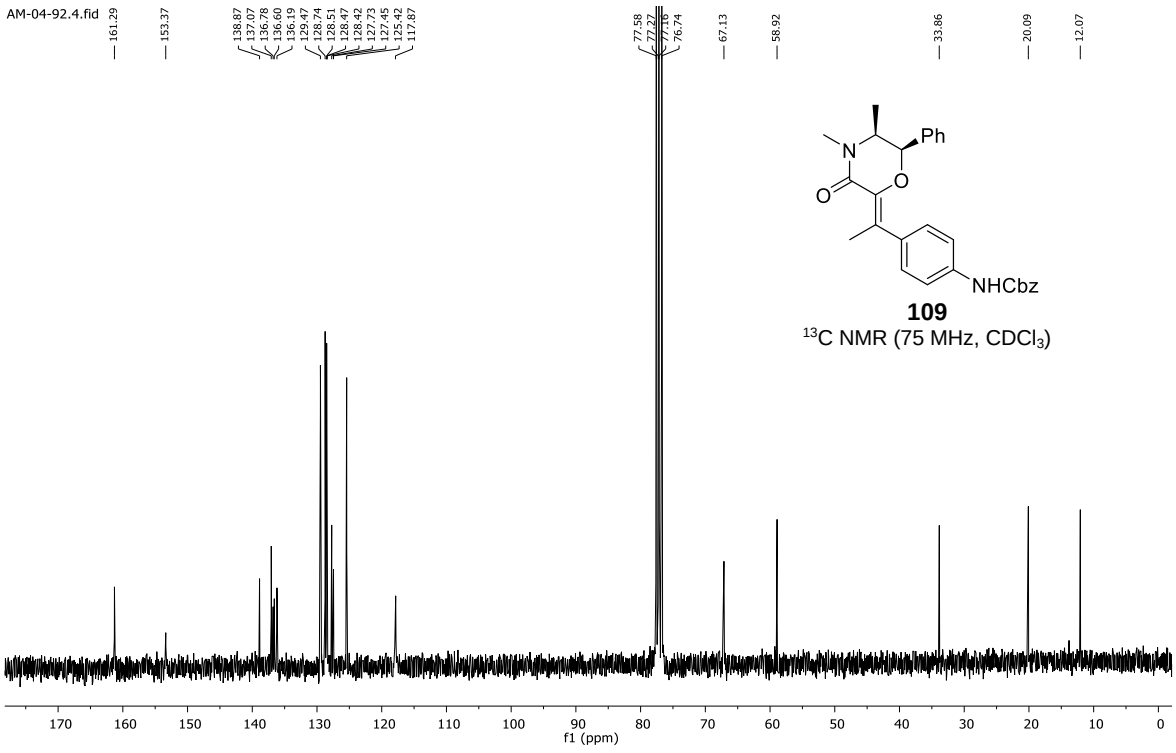
108

^{13}C NMR (75 MHz, $CDCl_3$)



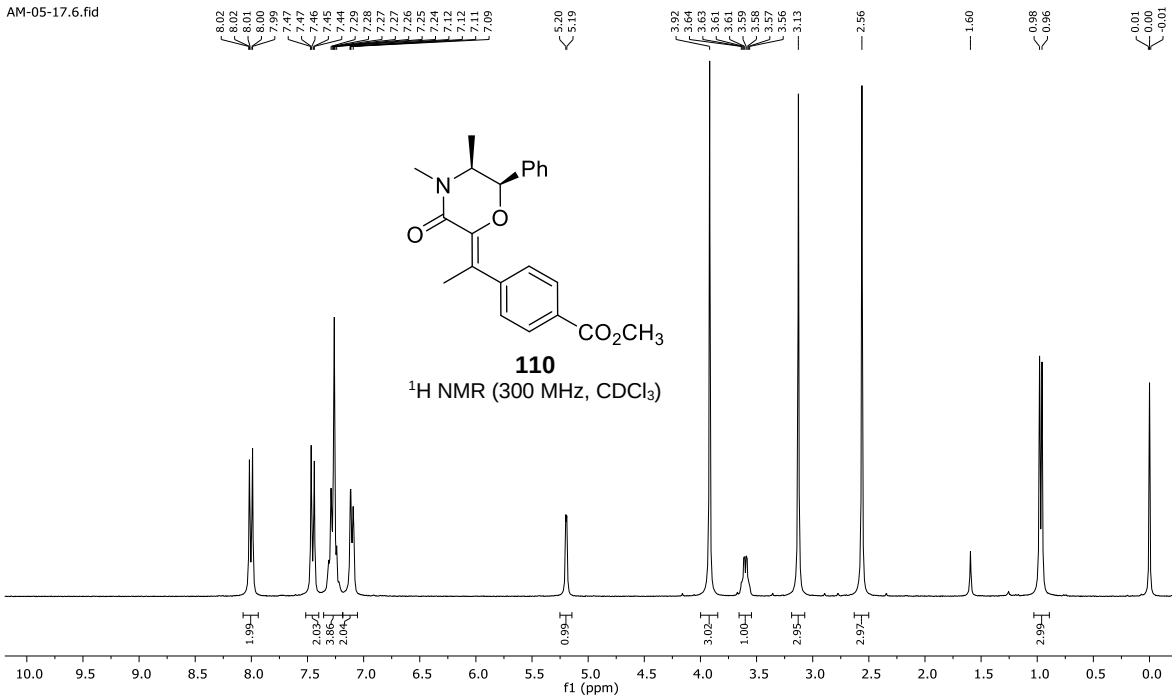
109

^{1}H NMR (300 MHz, $CDCl_3$)



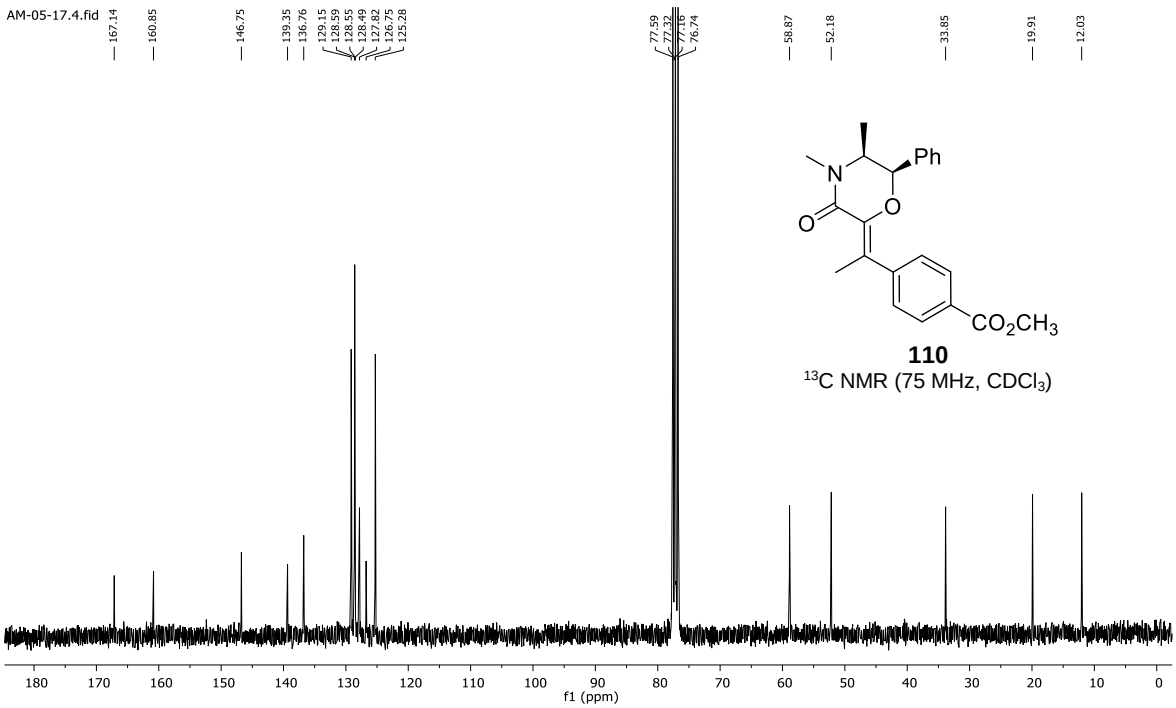
109

^{13}C NMR (75 MHz, $CDCl_3$)



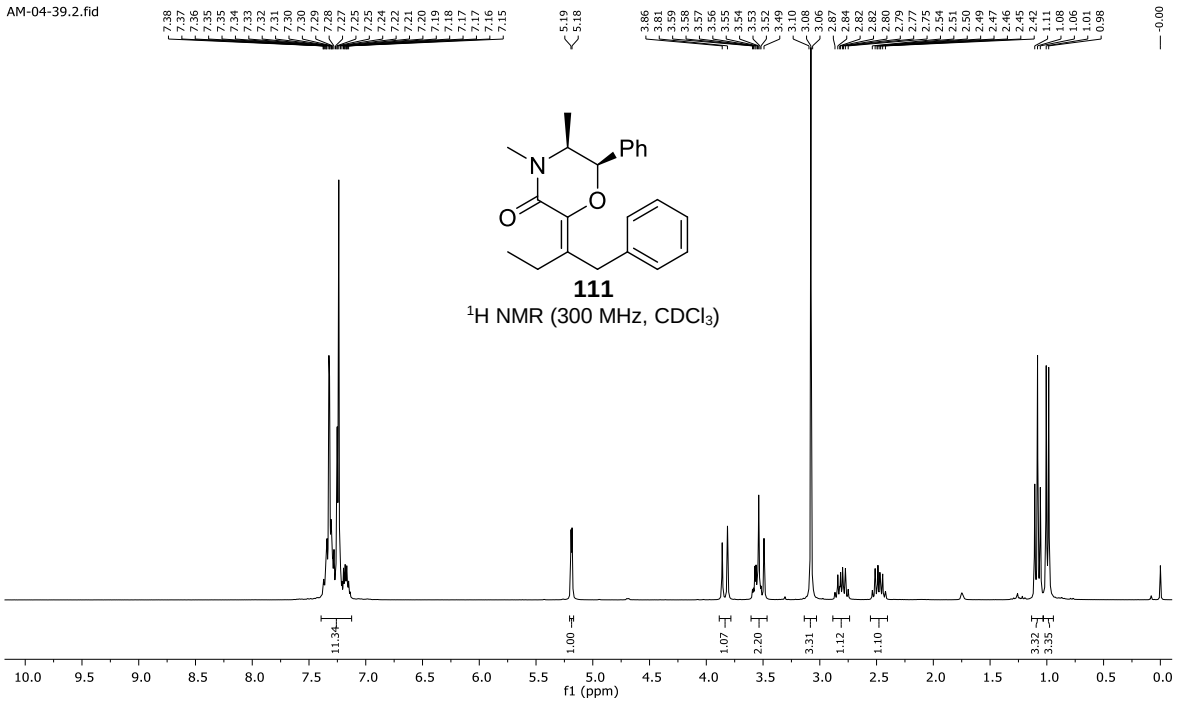
110

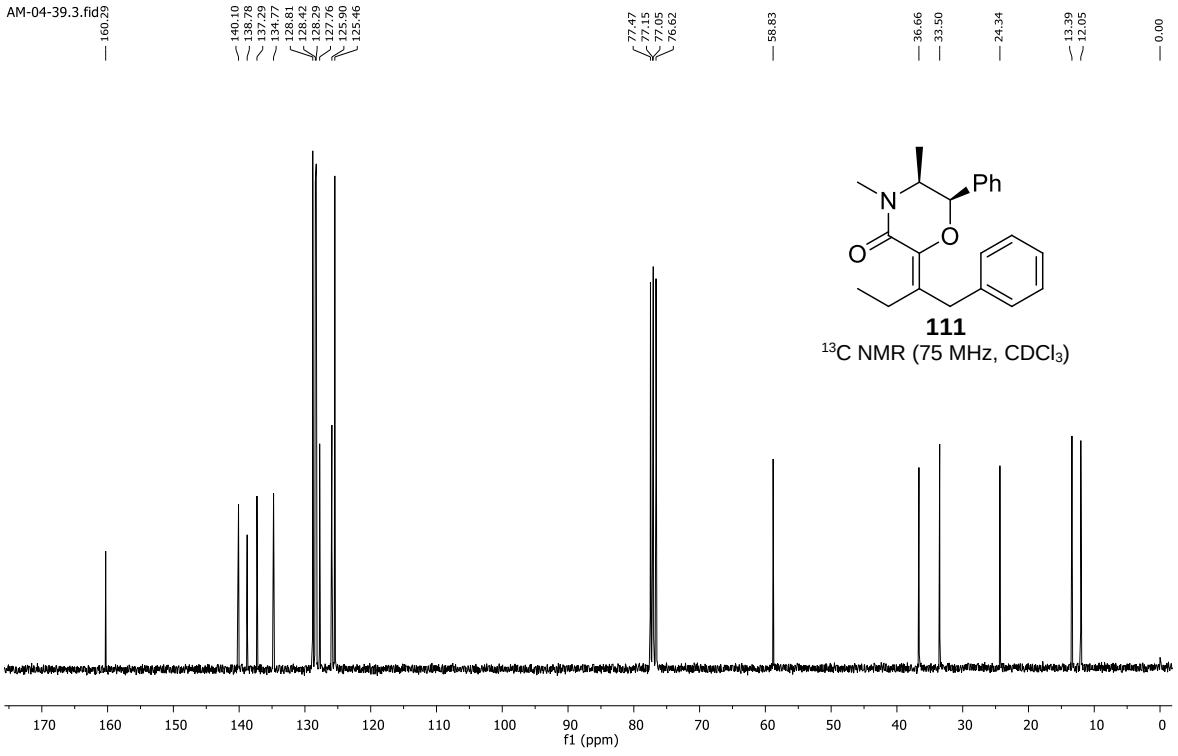
^{1}H NMR (300 MHz, $CDCl_3$)

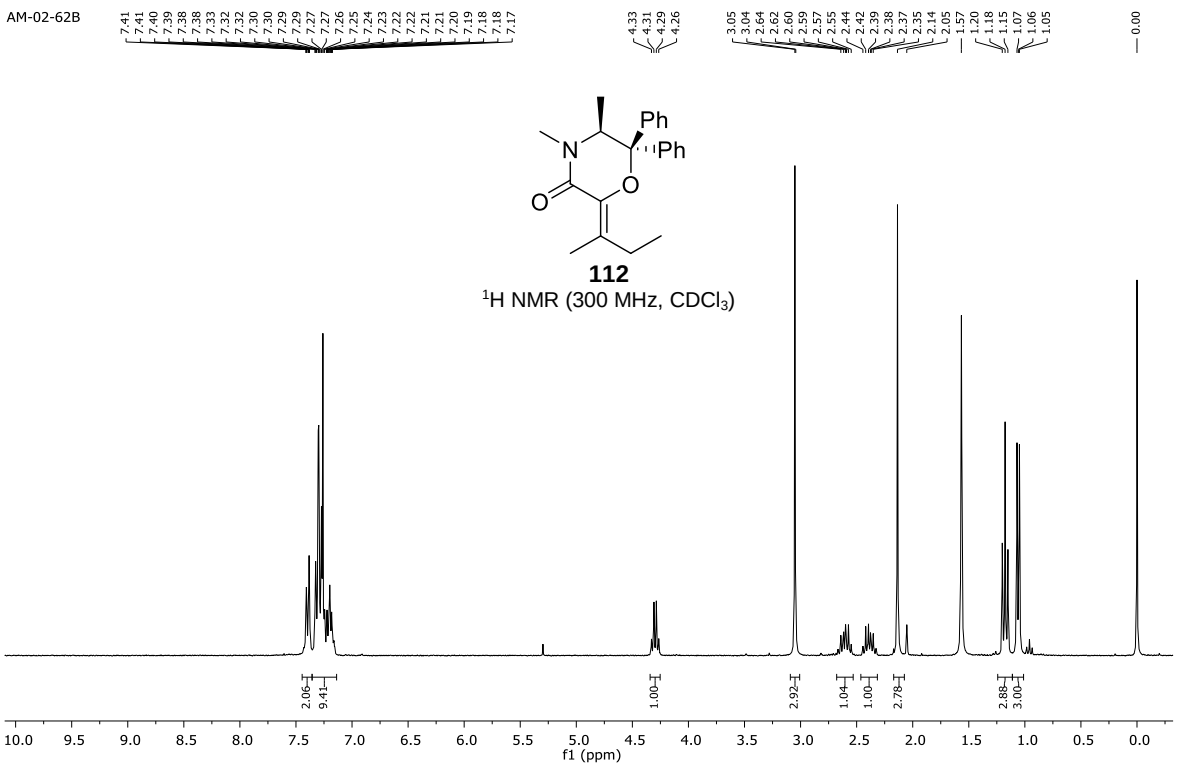


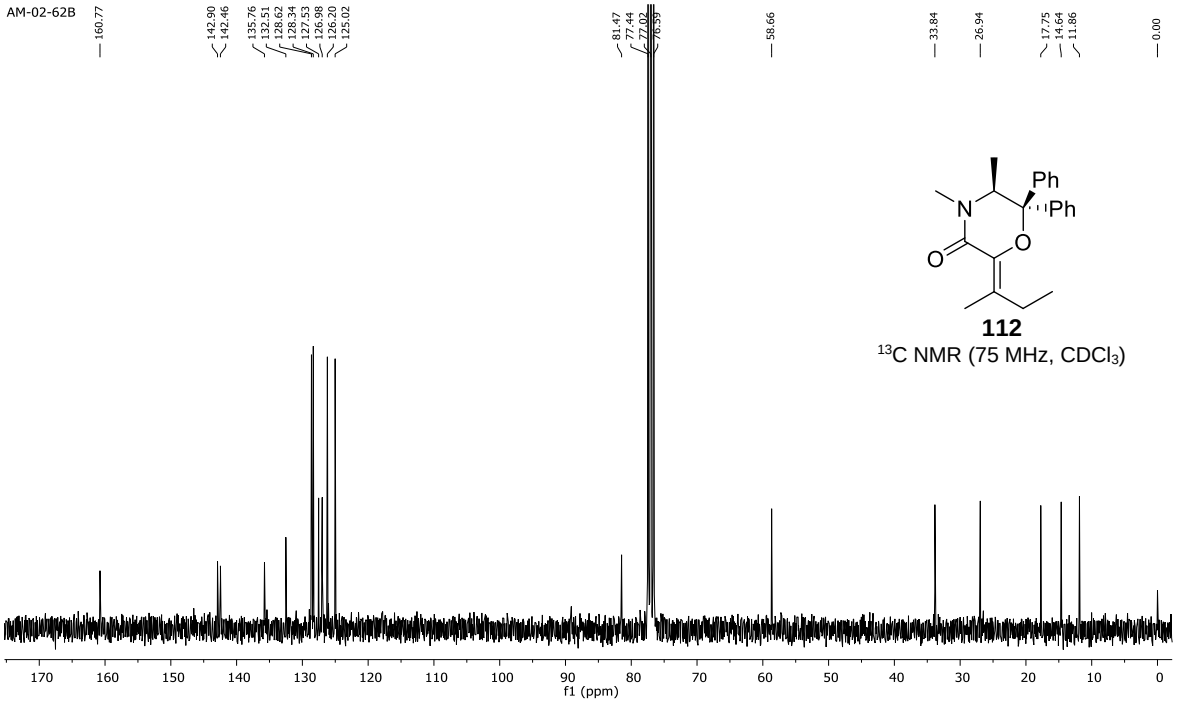
110

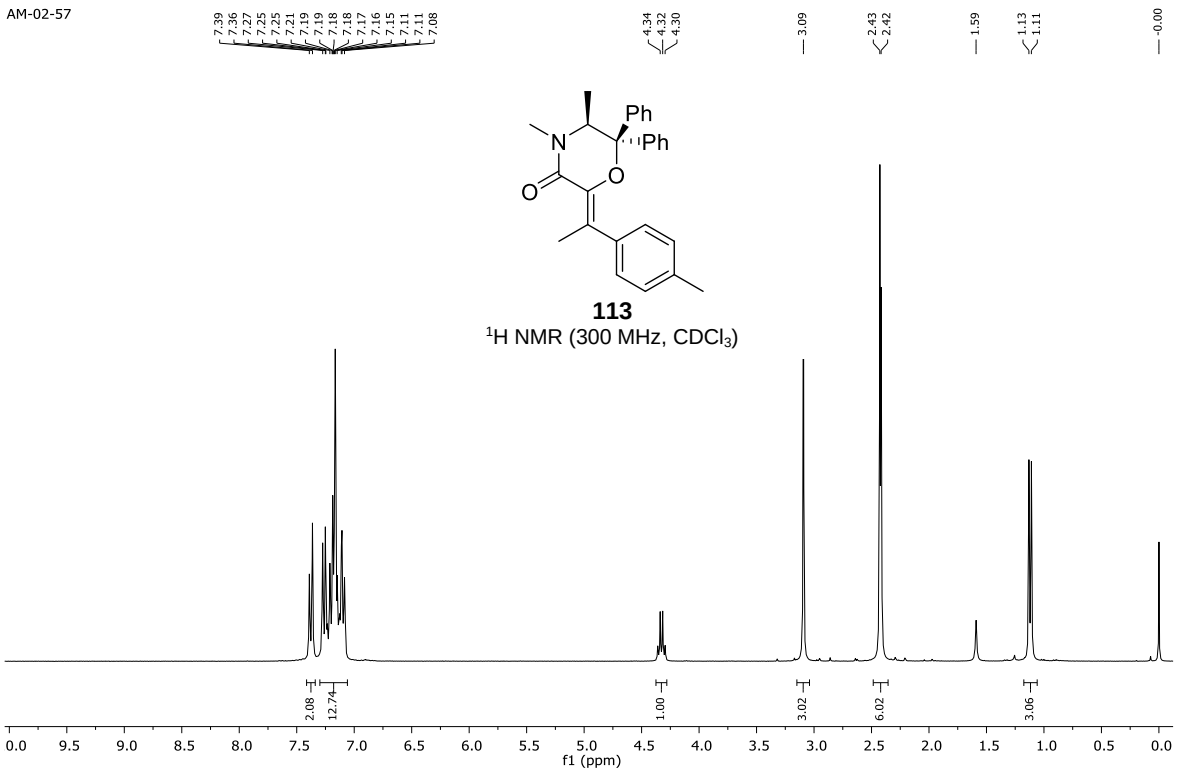
^{13}C NMR (75 MHz, $CDCl_3$)


AM-04-39.2.fid
Ph
N
O
O
111
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-04-39.3.fid
Ph
N
O
O
111
13C NMR (75 MHz, CDCl3)
f1 (ppm)

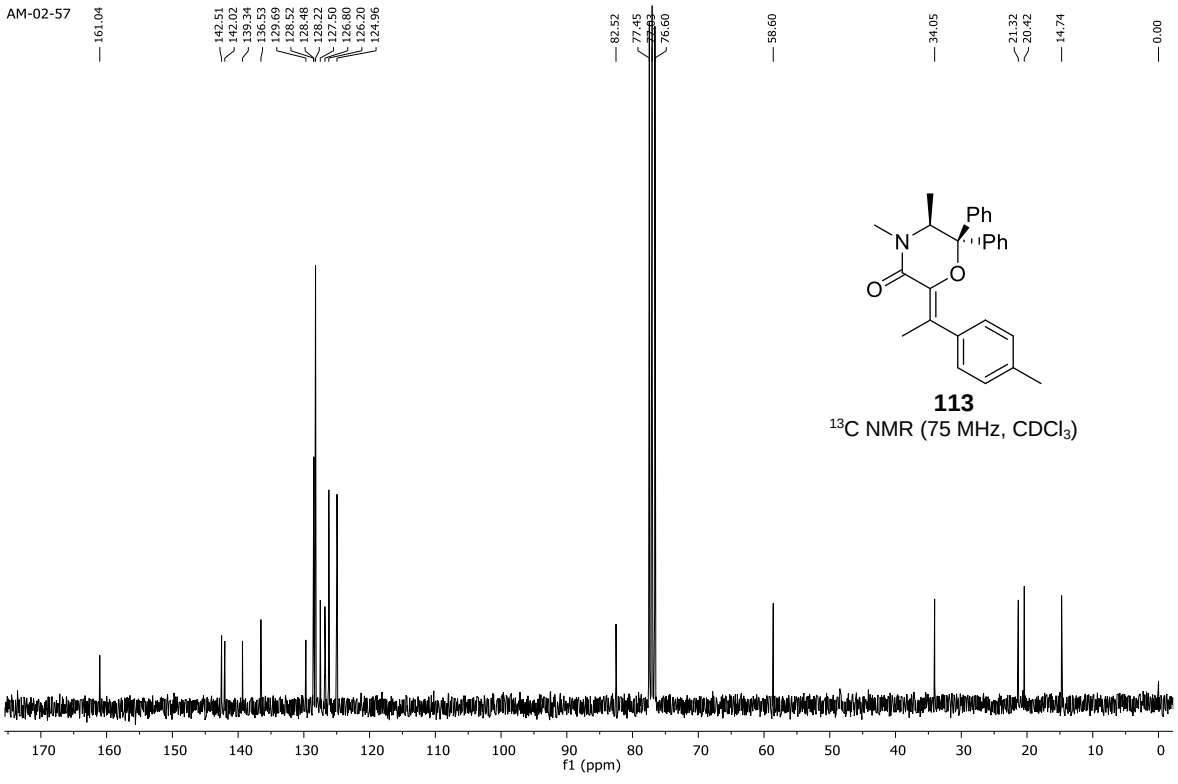

AM-02-62B
Ph
Ph
N
O
O
112
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-02-62B
Ph
Ph
N
O
O
112
13C NMR (75 MHz, CDCl3)
f1 (ppm)



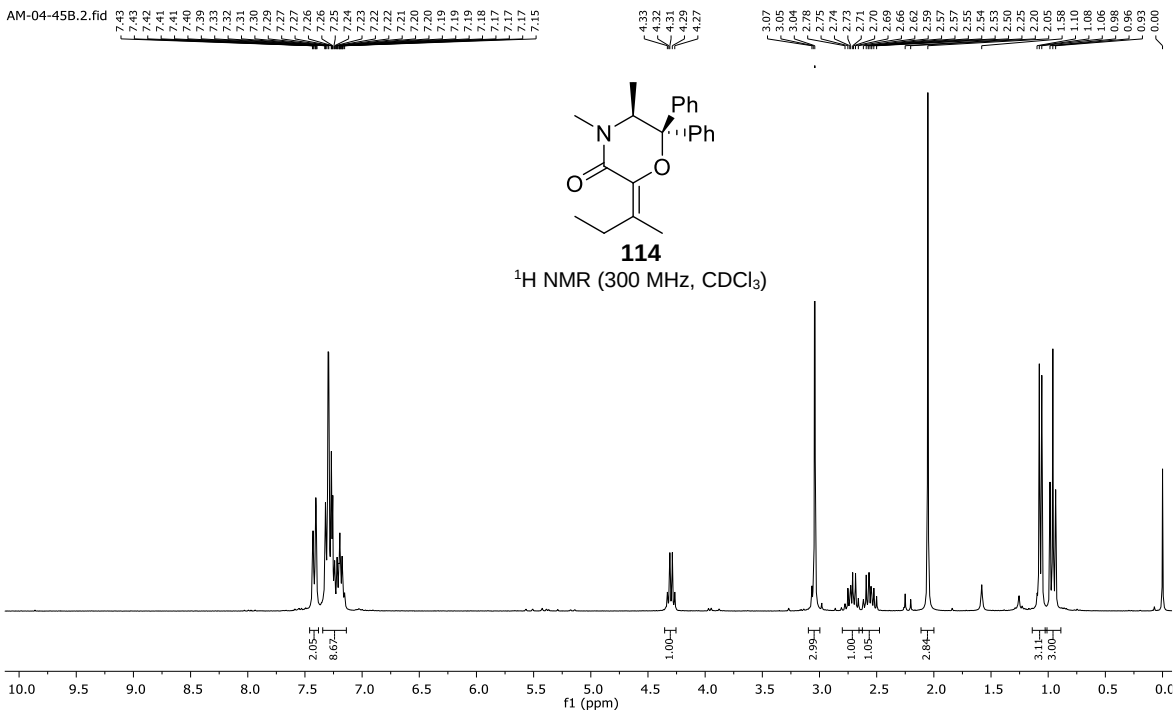
113

^{1}H NMR (300 MHz, $CDCl_3$)



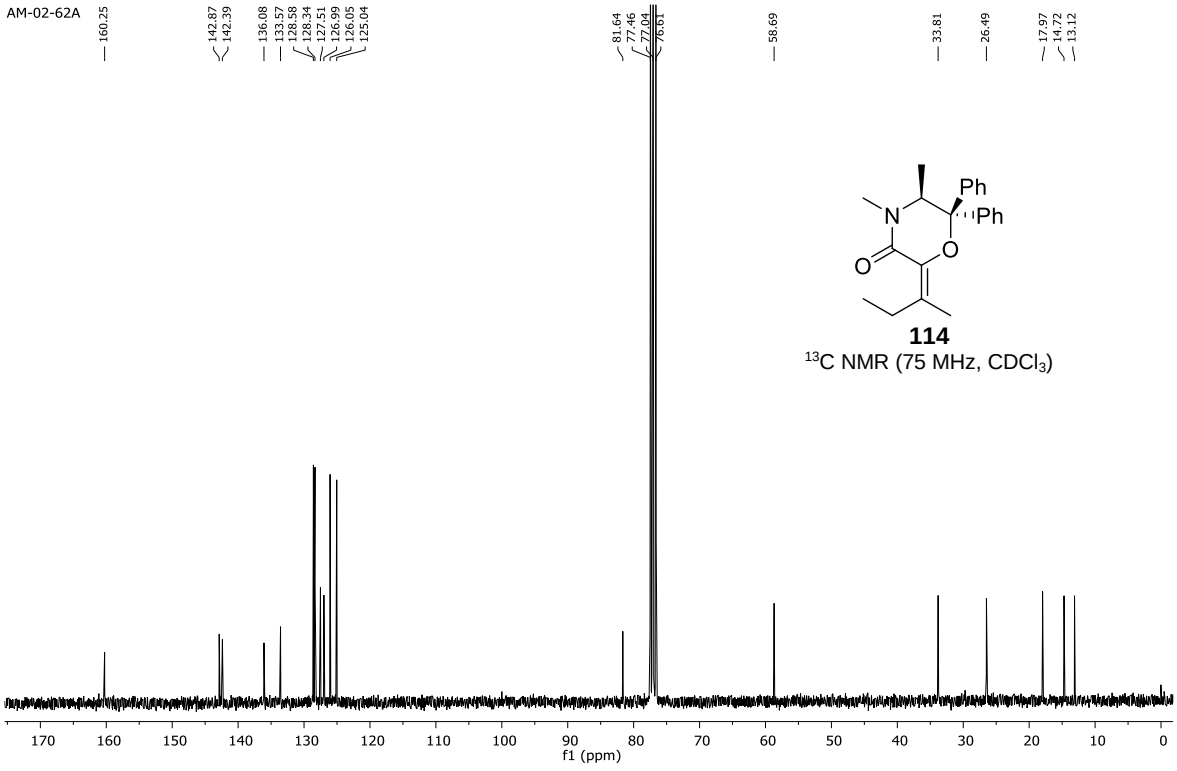
113

^{13}C NMR (75 MHz, $CDCl_3$)



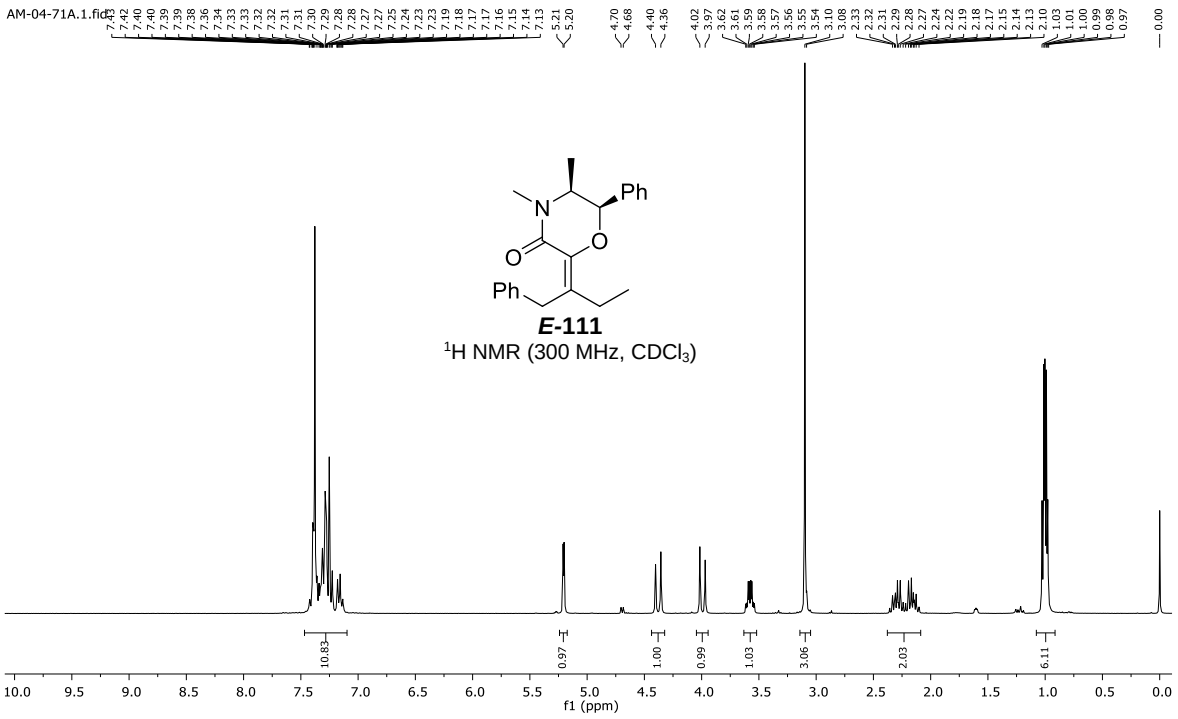
114

^{1}H NMR (300 MHz, $CDCl_3$)



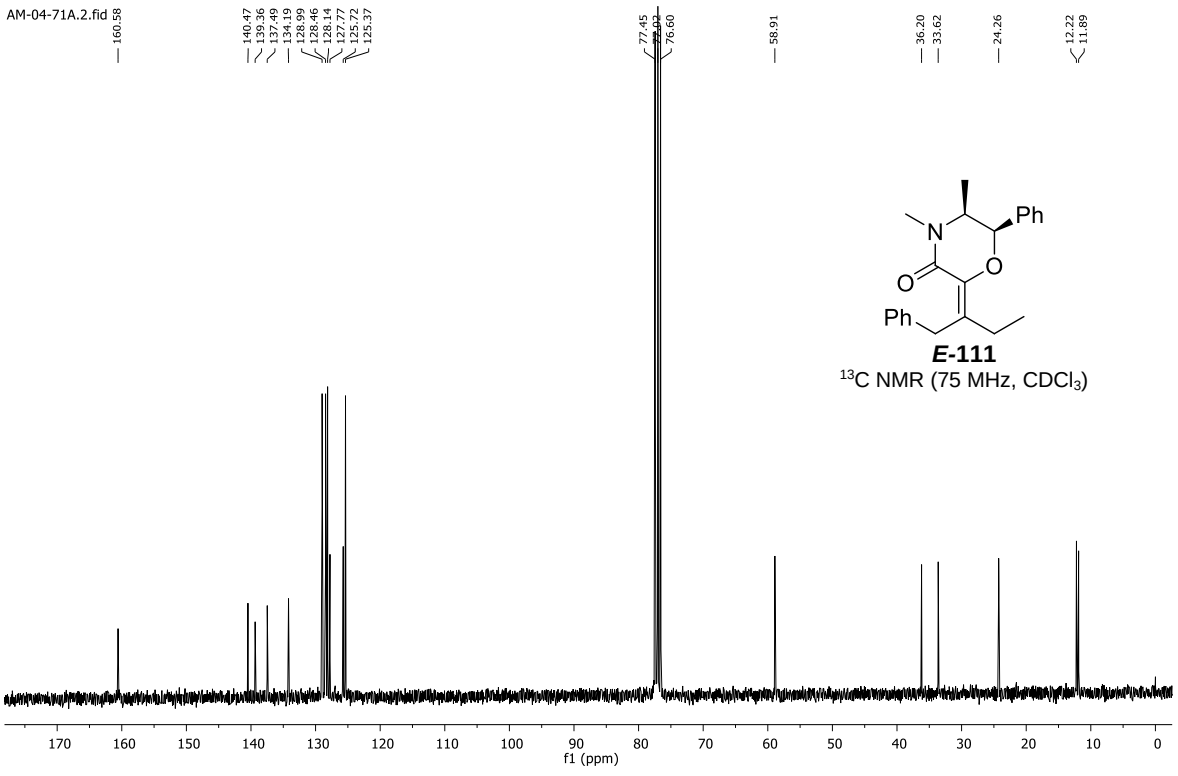
114

^{13}C NMR (75 MHz, $CDCl_3$)



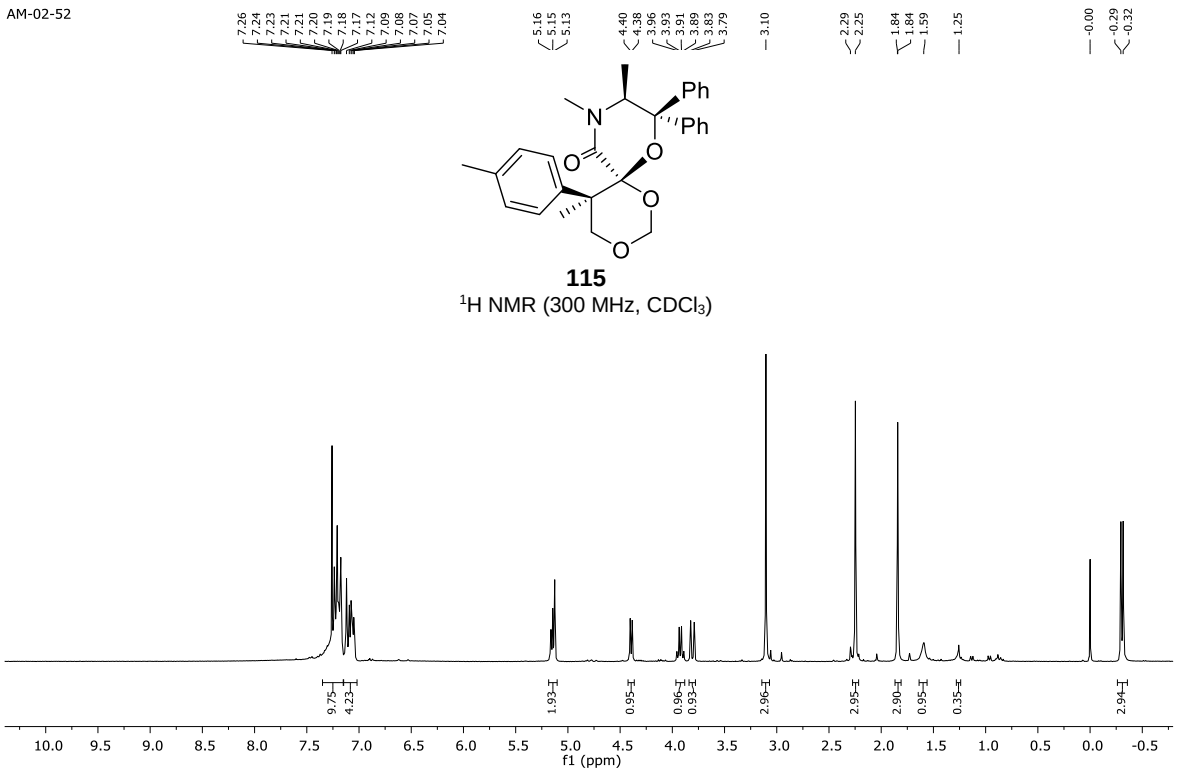
***E*-111**

^{1}H NMR (300 MHz, $CDCl_3$)



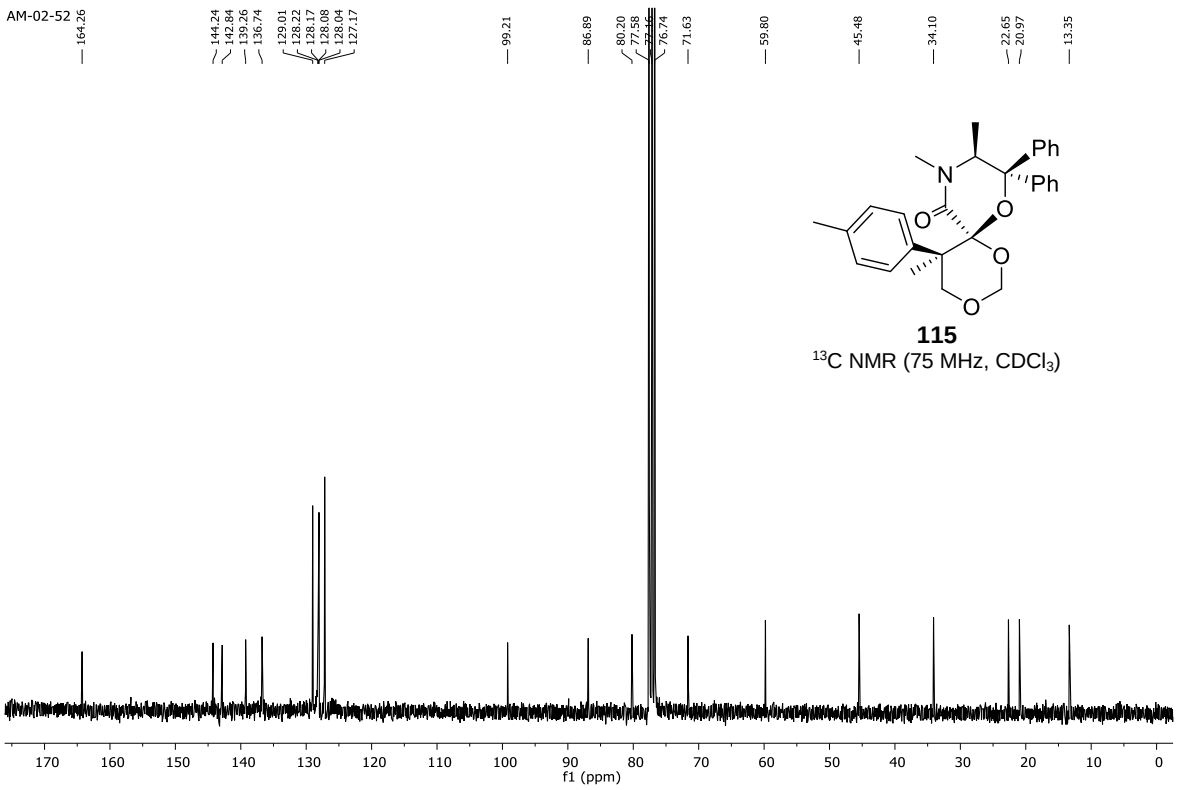
***E*-111**

^{13}C NMR (75 MHz, $CDCl_3$)



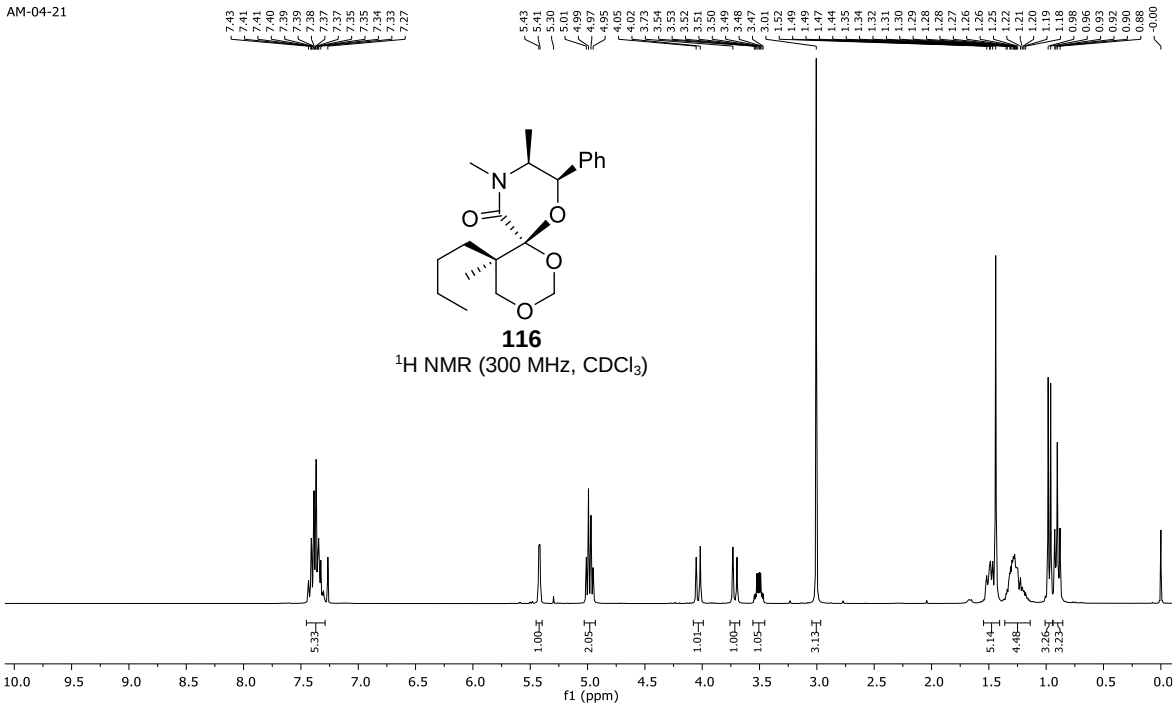
115

^{1}H NMR (300 MHz, $CDCl_3$)



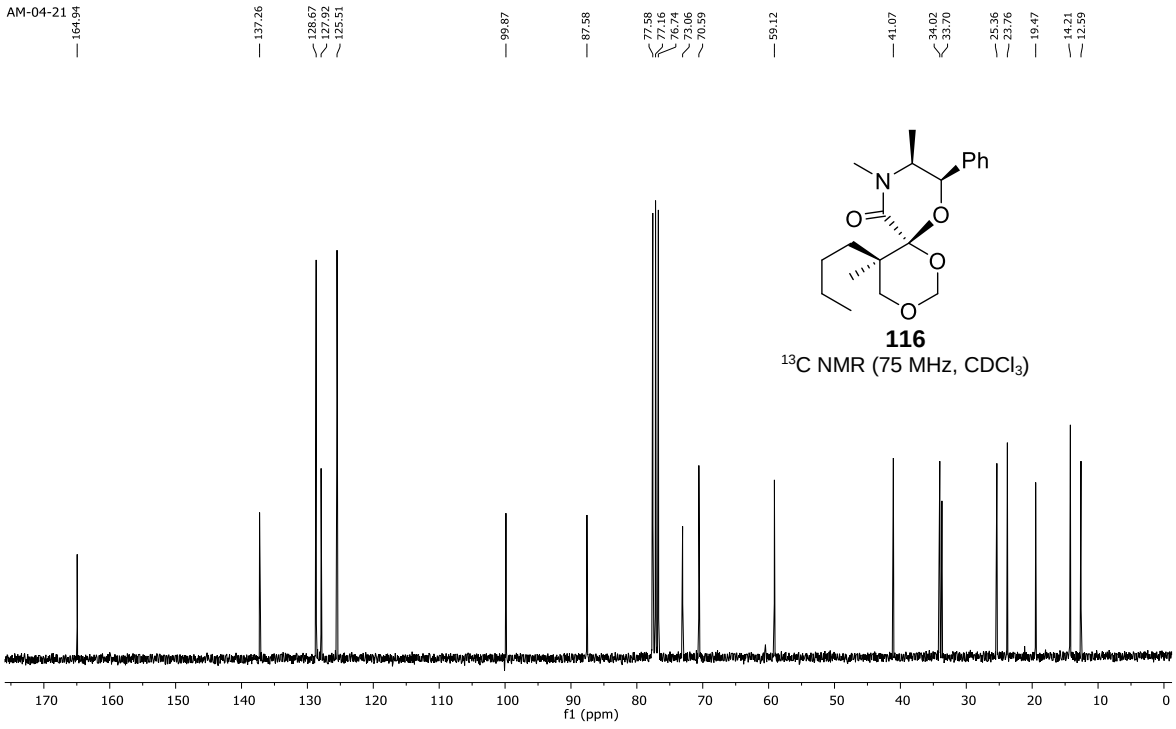
115

^{13}C NMR (75 MHz, $CDCl_3$)



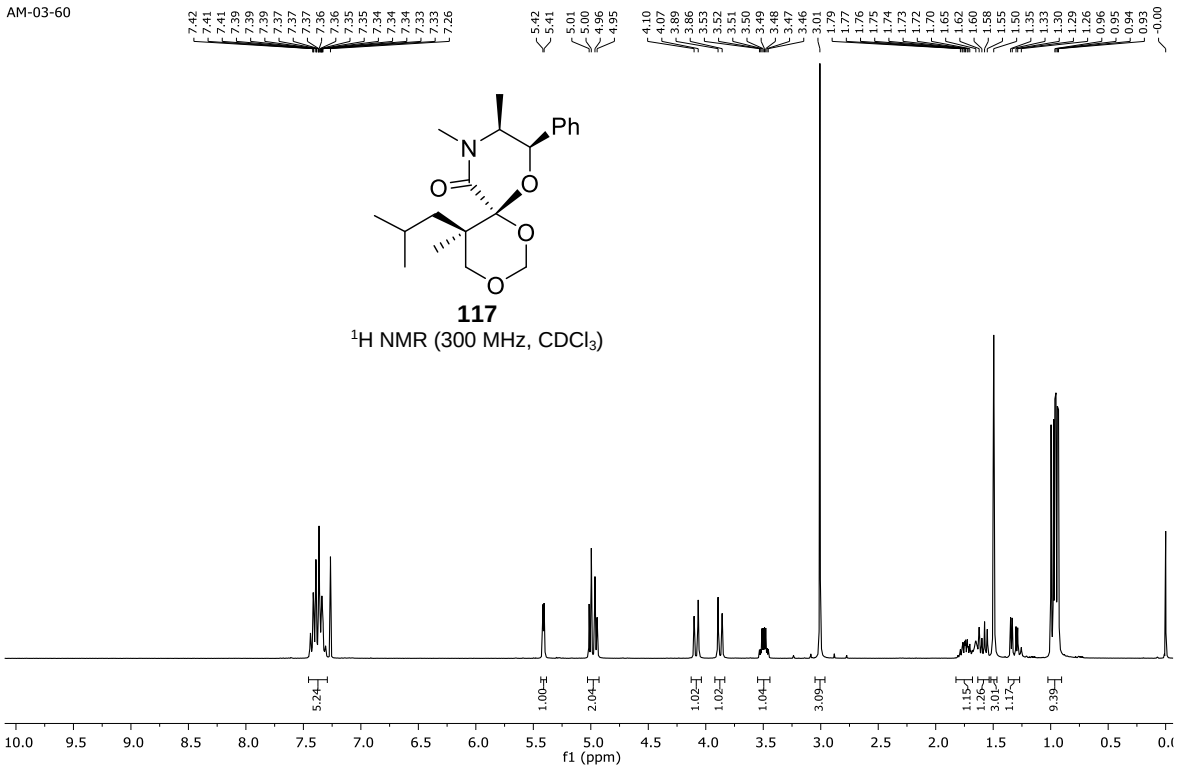
116

^{1}H NMR (300 MHz, $CDCl_3$)



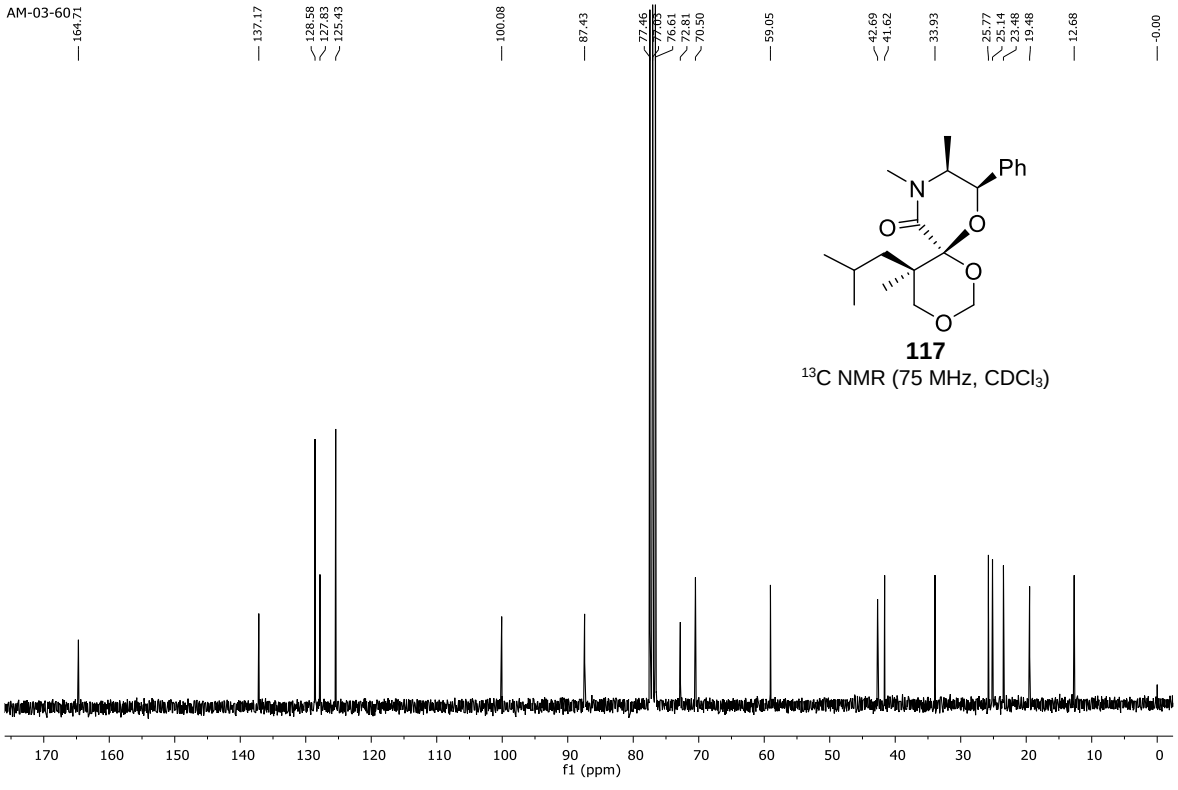
116

^{13}C NMR (75 MHz, $CDCl_3$)



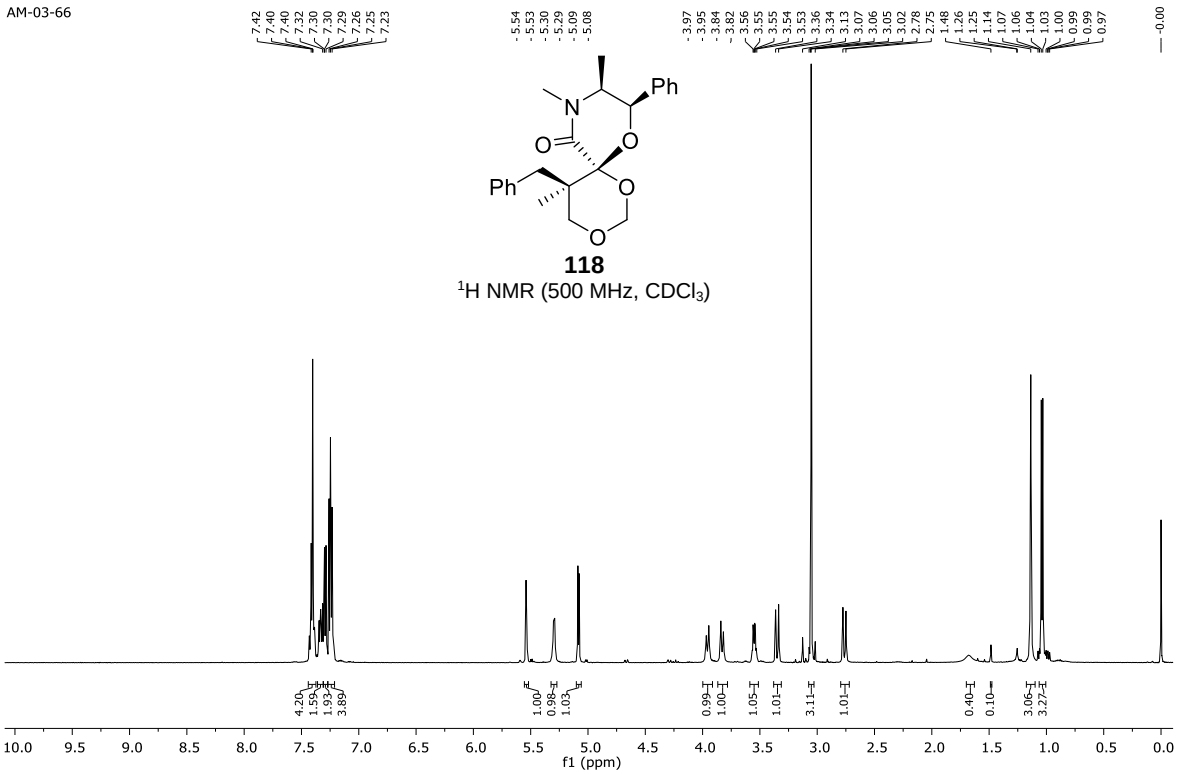
117

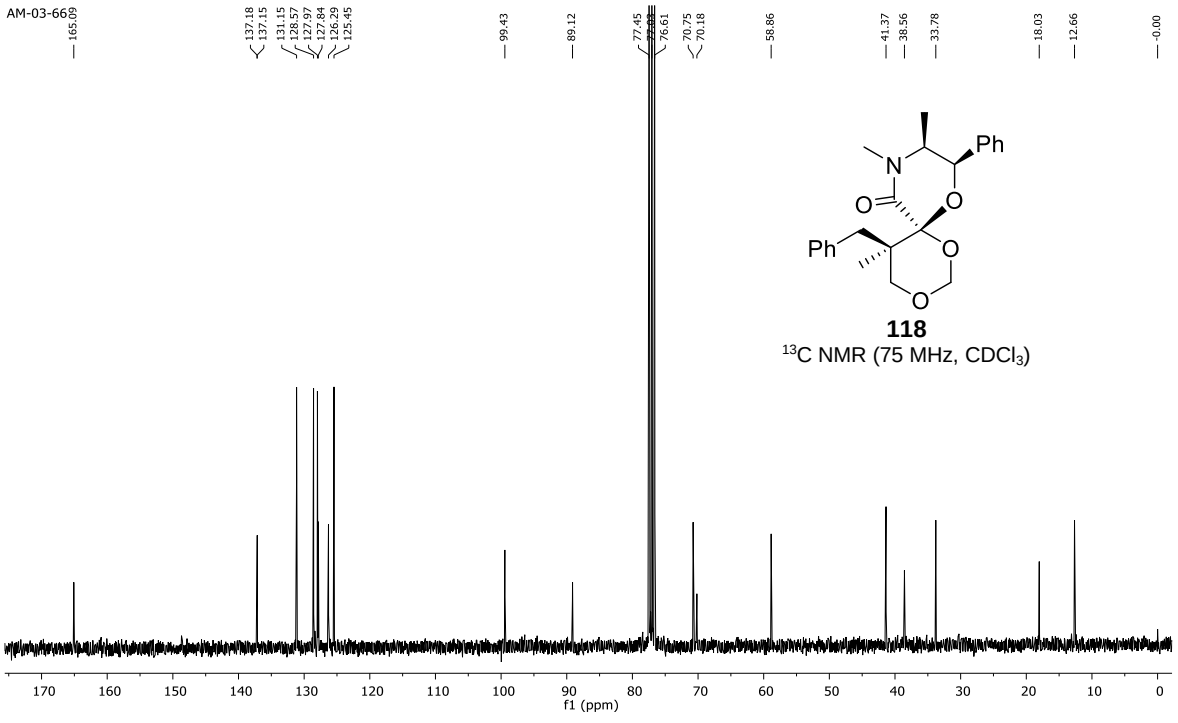
^{1}H NMR (300 MHz, $CDCl_3$)

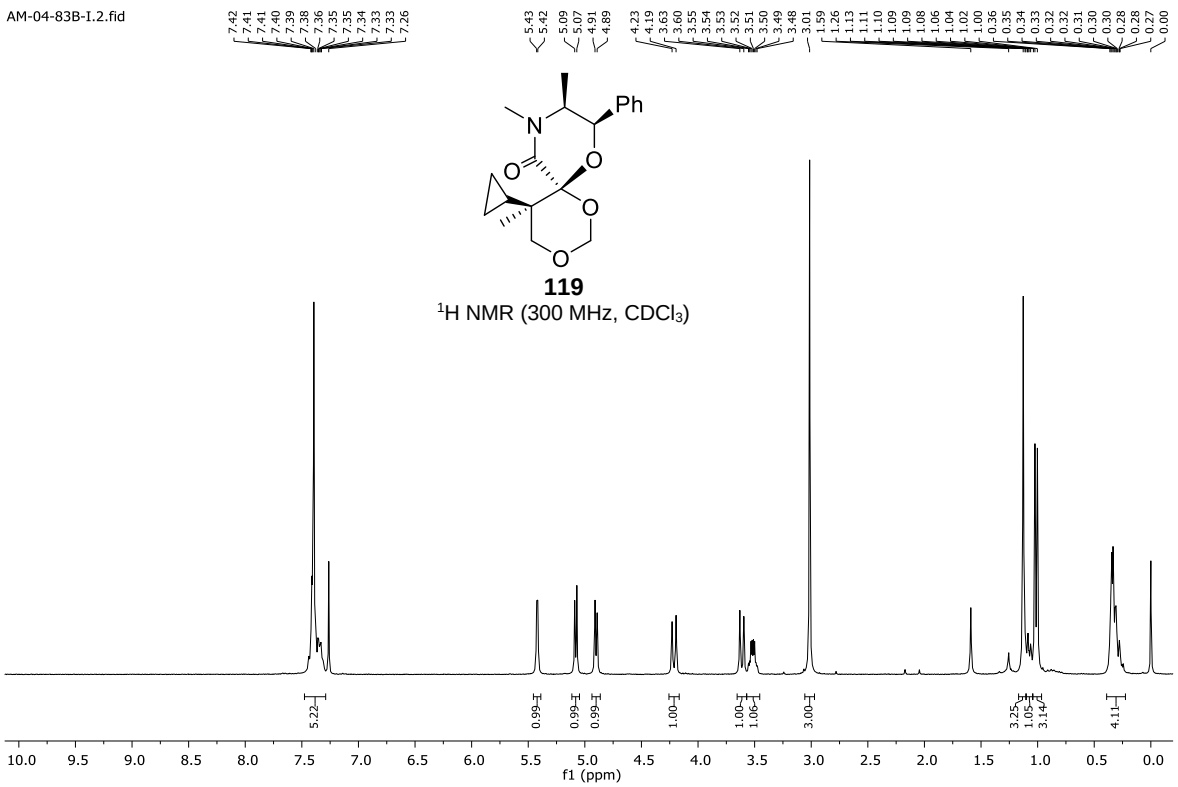


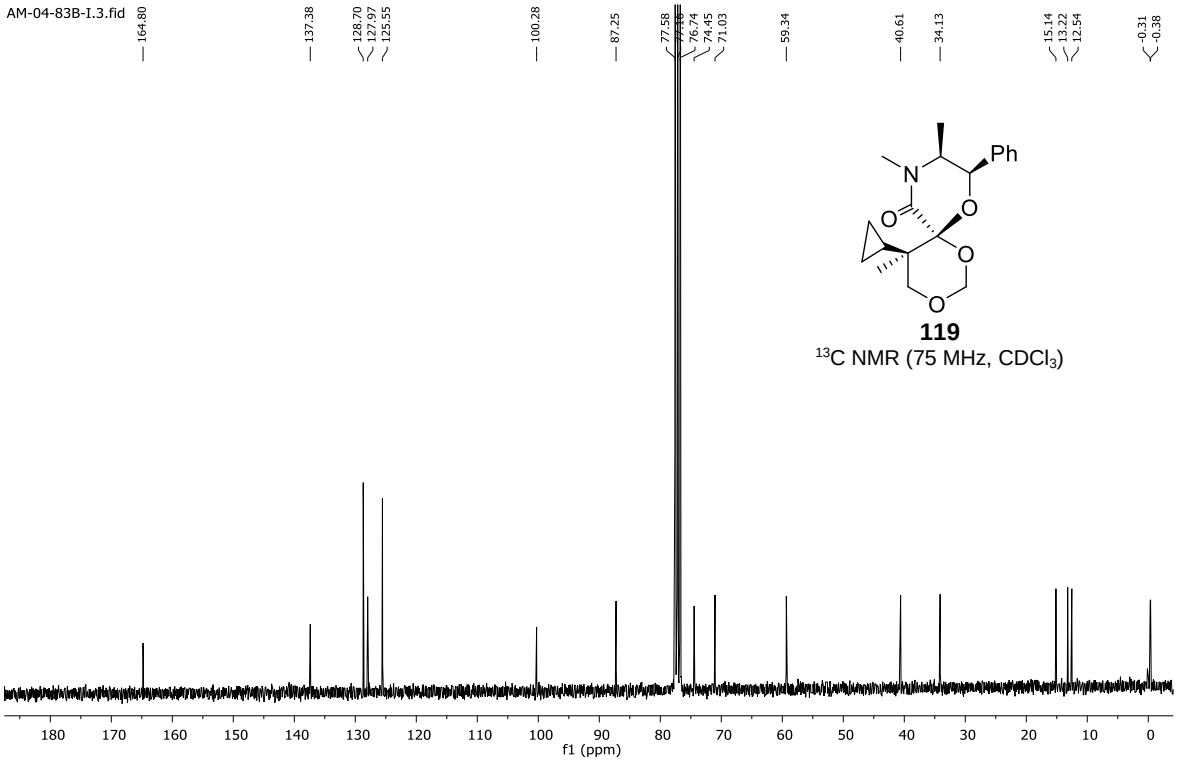
117

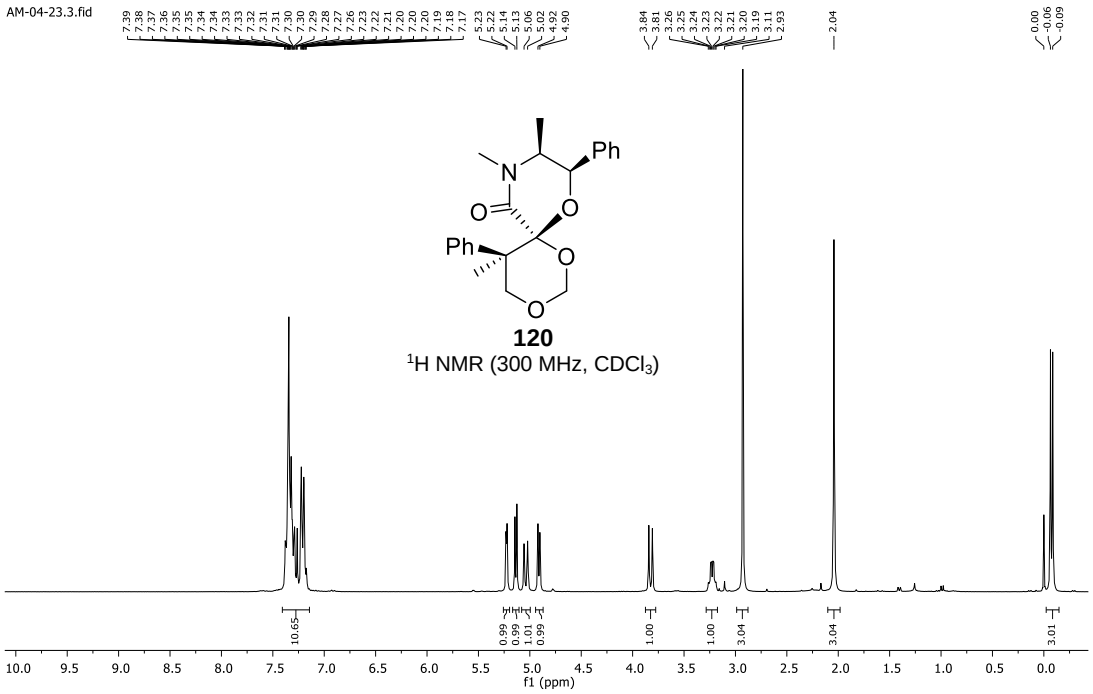
^{13}C NMR (75 MHz, $CDCl_3$)

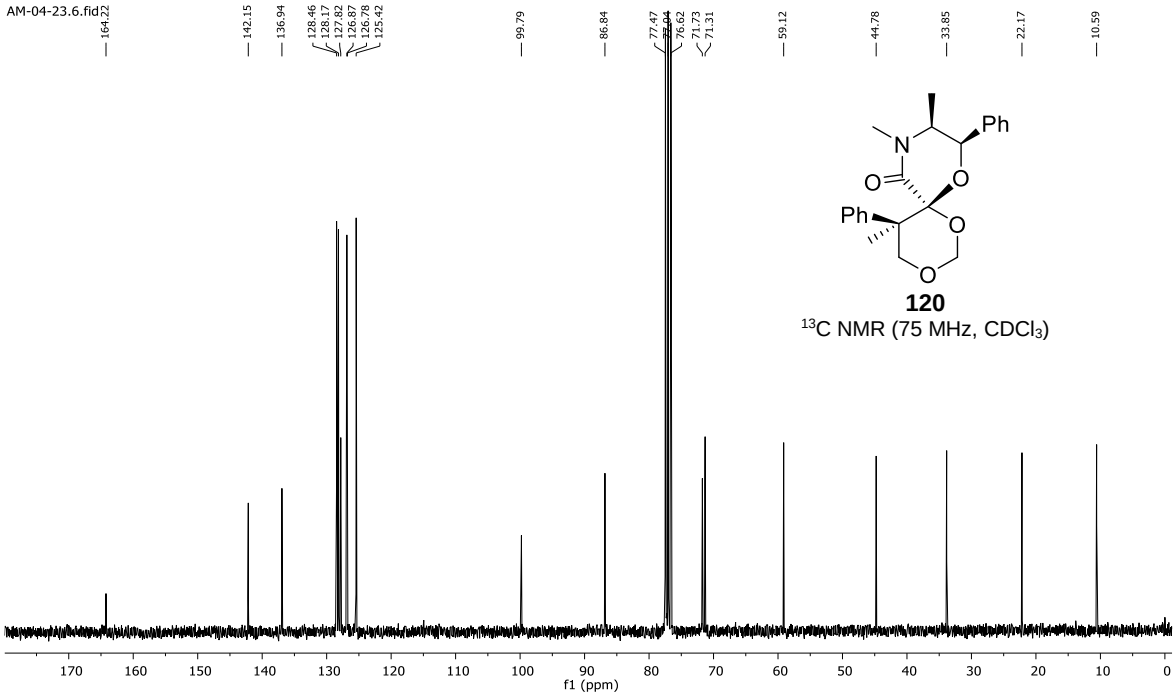

AM-03-66
Ph
N
O
O
Ph
O
O
118
1H NMR (500 MHz, CDCl3)
f1 (ppm)


AM-03-66
Ph
N
O
O
Ph
O
O
118
13C NMR (75 MHz, CDCl3)
f1 (ppm)


AM-04-83B-I.2.fid
Ph
N
O
O
O
O
119
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-04-83B-I.3.fid
Ph
N
O
O
O
O
119
13C NMR (75 MHz, CDCl3)
f1 (ppm)


AM-04-23.3.fid
Ph
N
O
O
Ph
O
O
120
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-04-23.6.fid
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O
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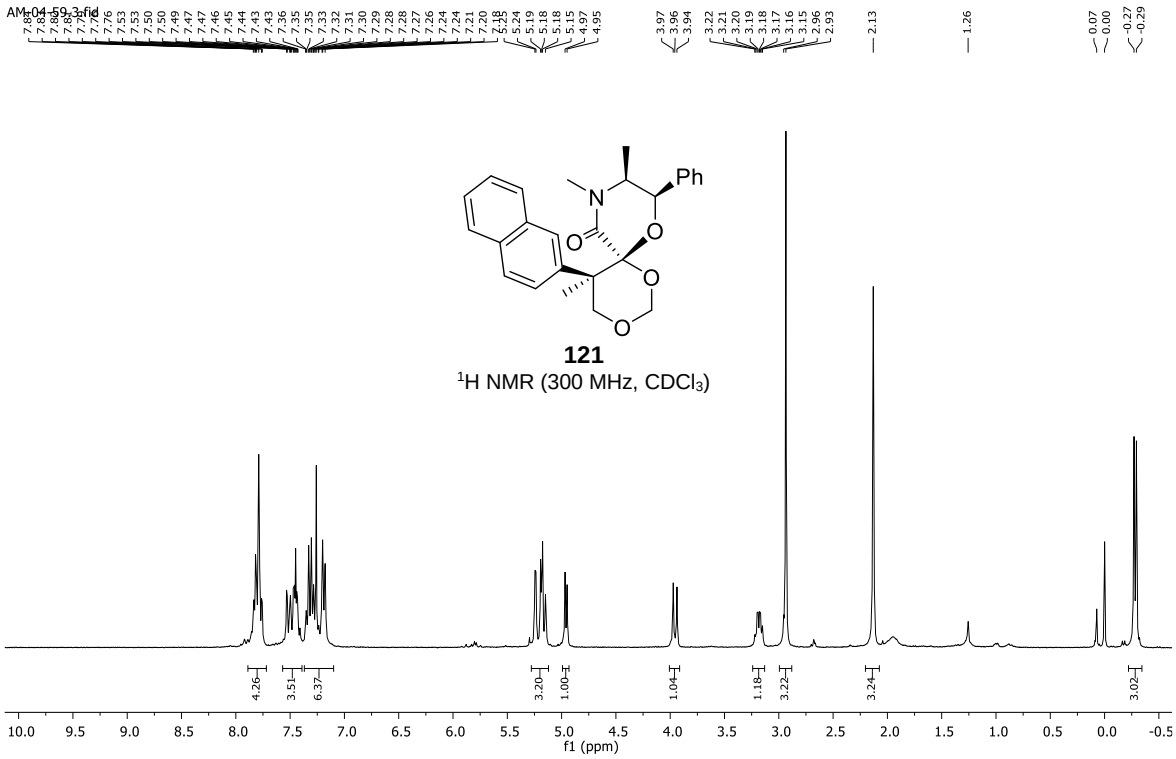
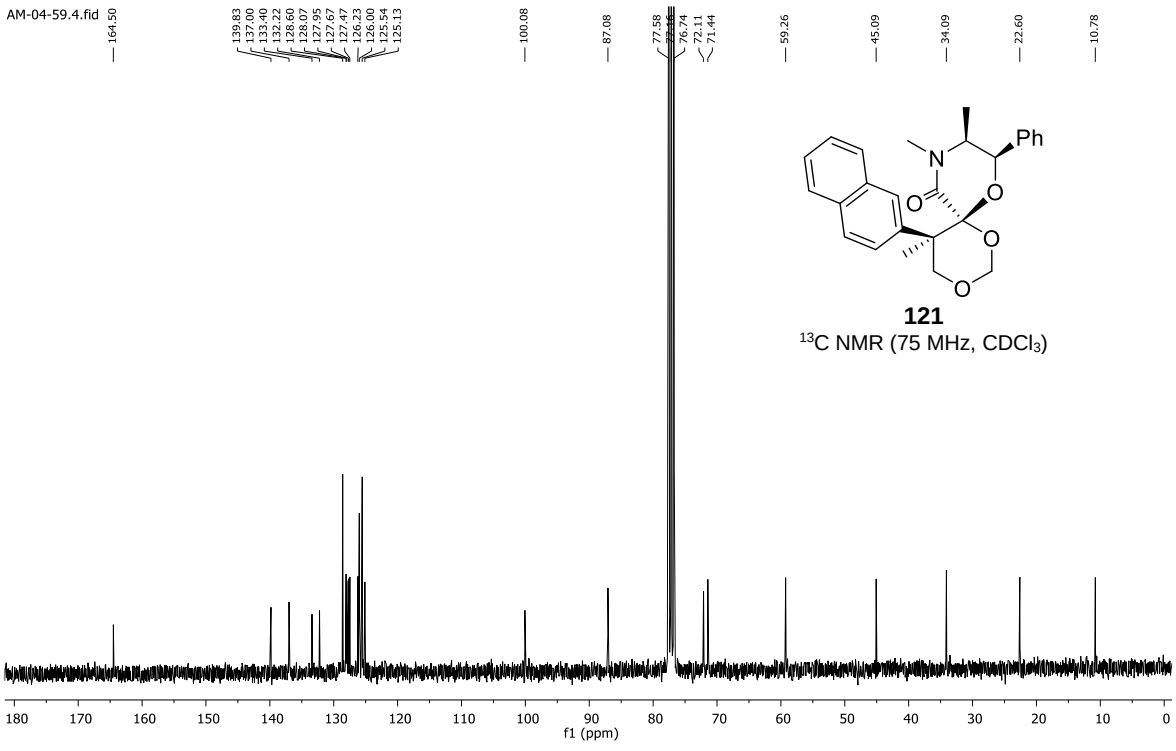
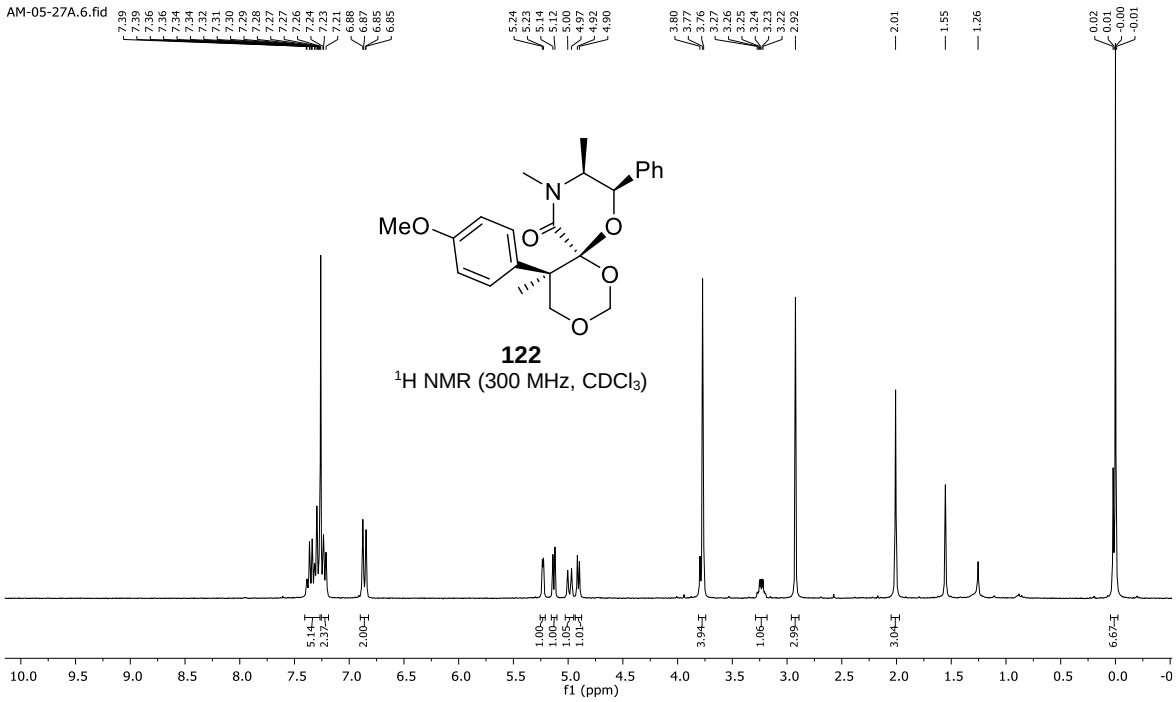
Ph
O
O
120
13C NMR (75 MHz, CDCl3)
f1 (ppm)

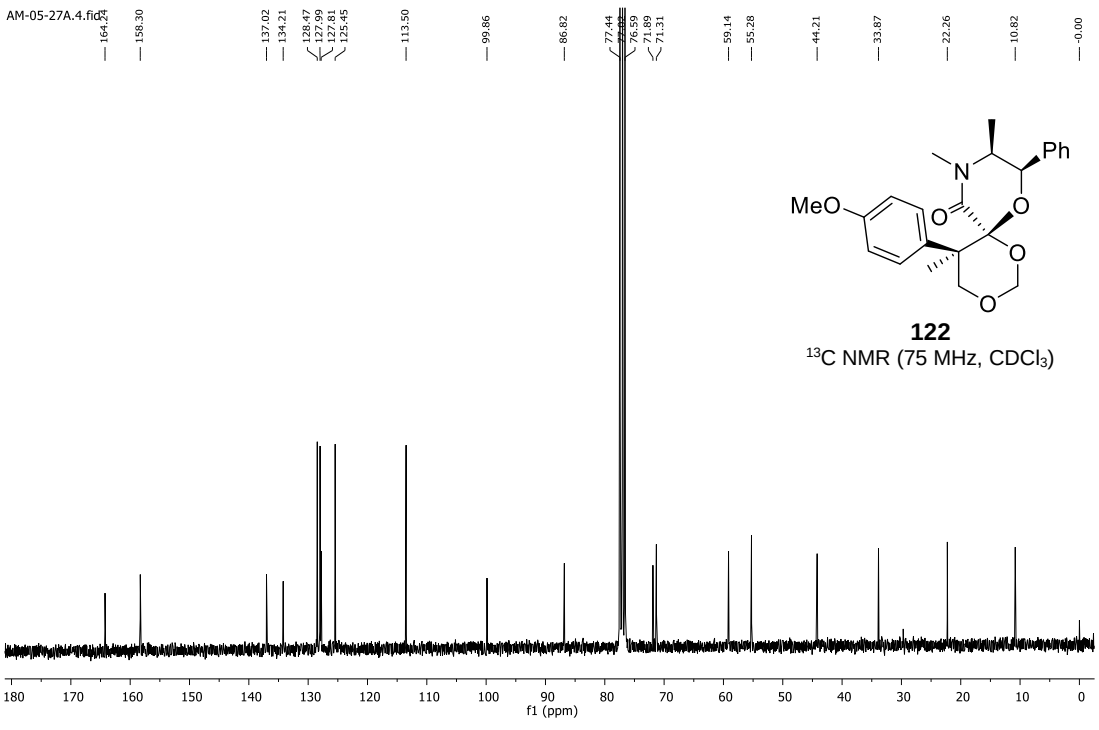

AM-04-59-3.fid
Ph
N
O
O
O
O
121
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-04-59.4.fid
Ph
N
O
O
O
O
121
13C NMR (75 MHz, CDCl3)
f1 (ppm)



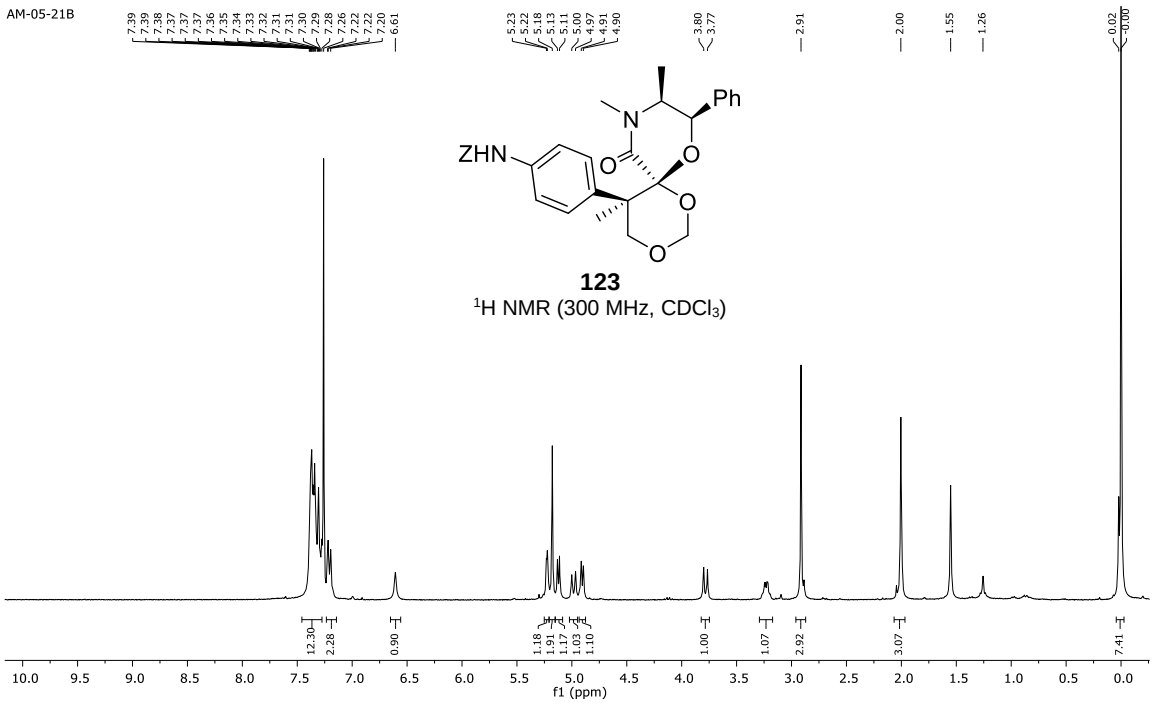
122

^{1}H NMR (300 MHz, $CDCl_3$)



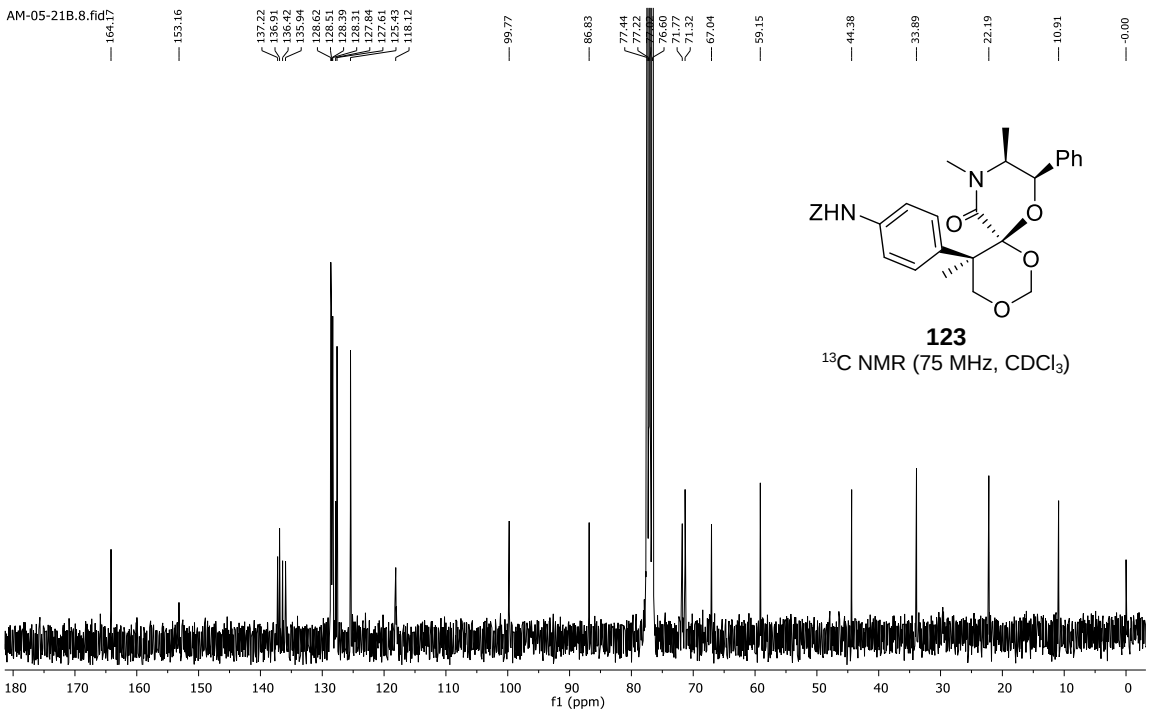
122

^{13}C NMR (75 MHz, $CDCl_3$)



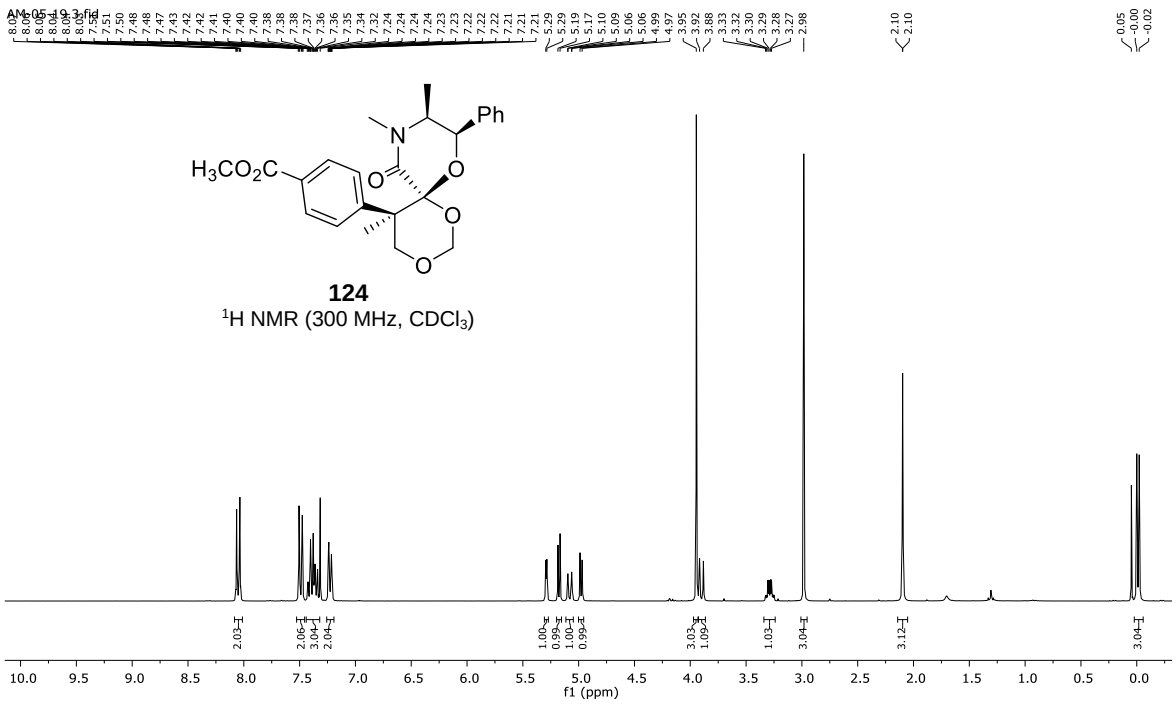
123

^{1}H NMR (300 MHz, $CDCl_3$)



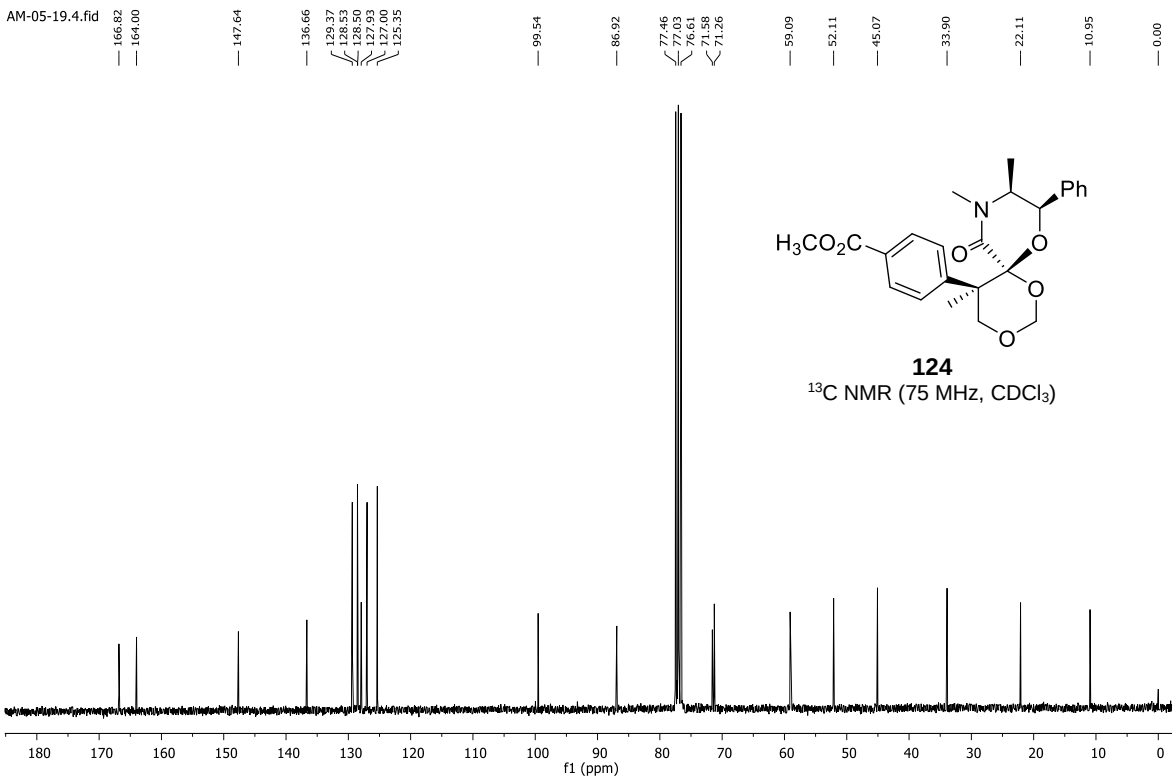
123

^{13}C NMR (75 MHz, $CDCl_3$)



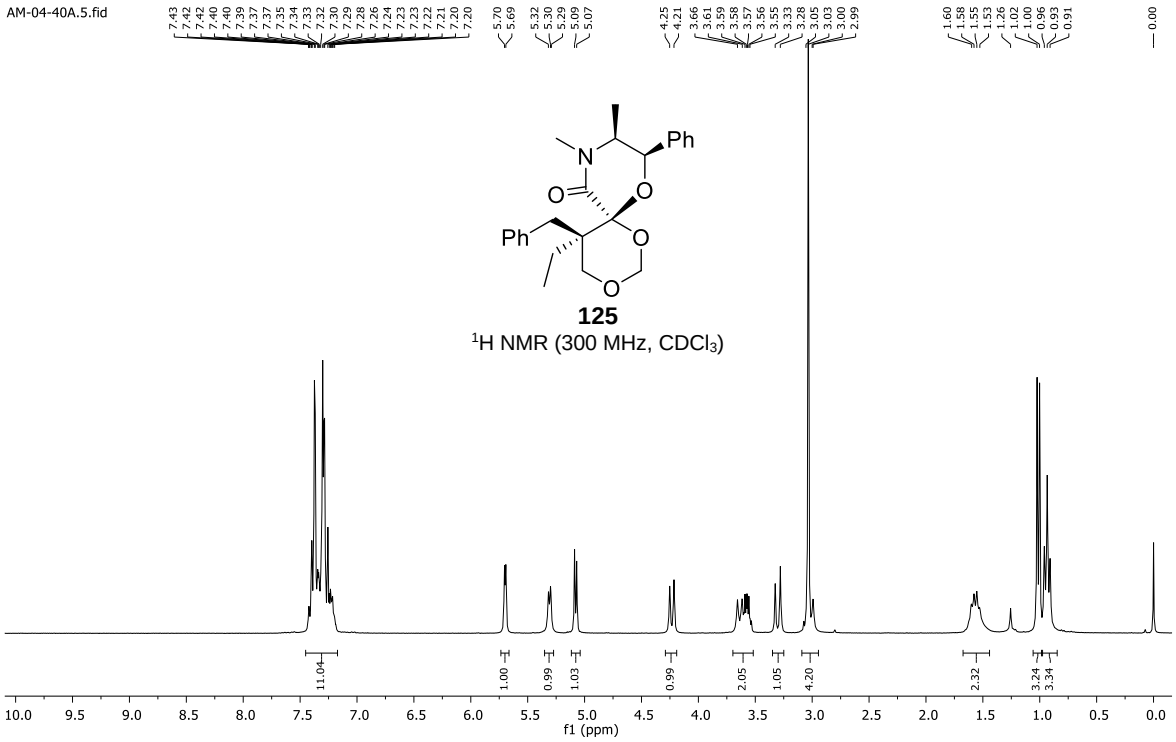
124

^{1}H NMR (300 MHz, $CDCl_3$)



124

^{13}C NMR (75 MHz, $CDCl_3$)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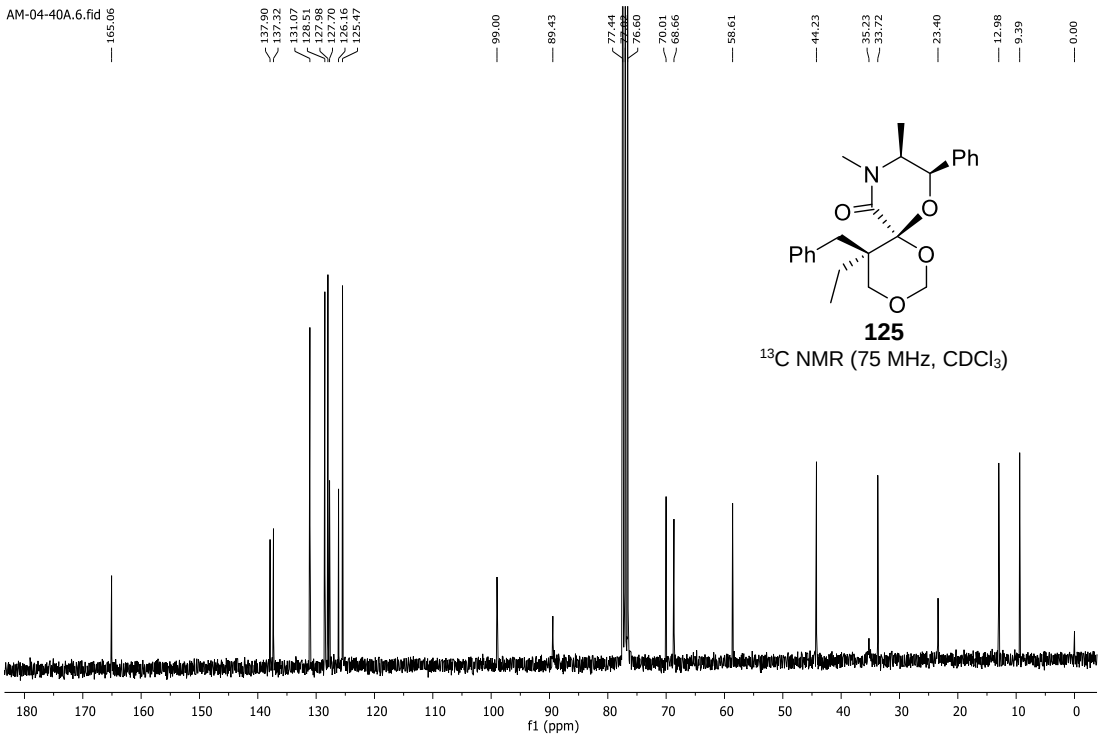
N
O
O
Ph
O
O
125
1H NMR (300 MHz, CDCl3)
f1 (ppm)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Ph
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Ph
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O
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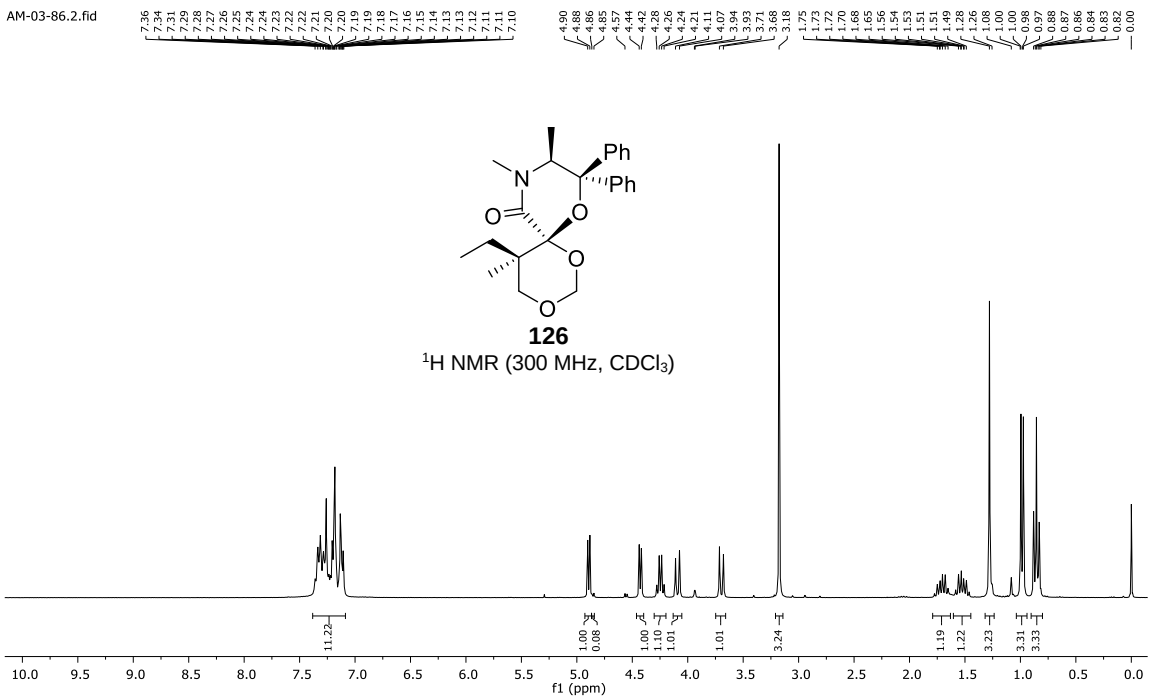
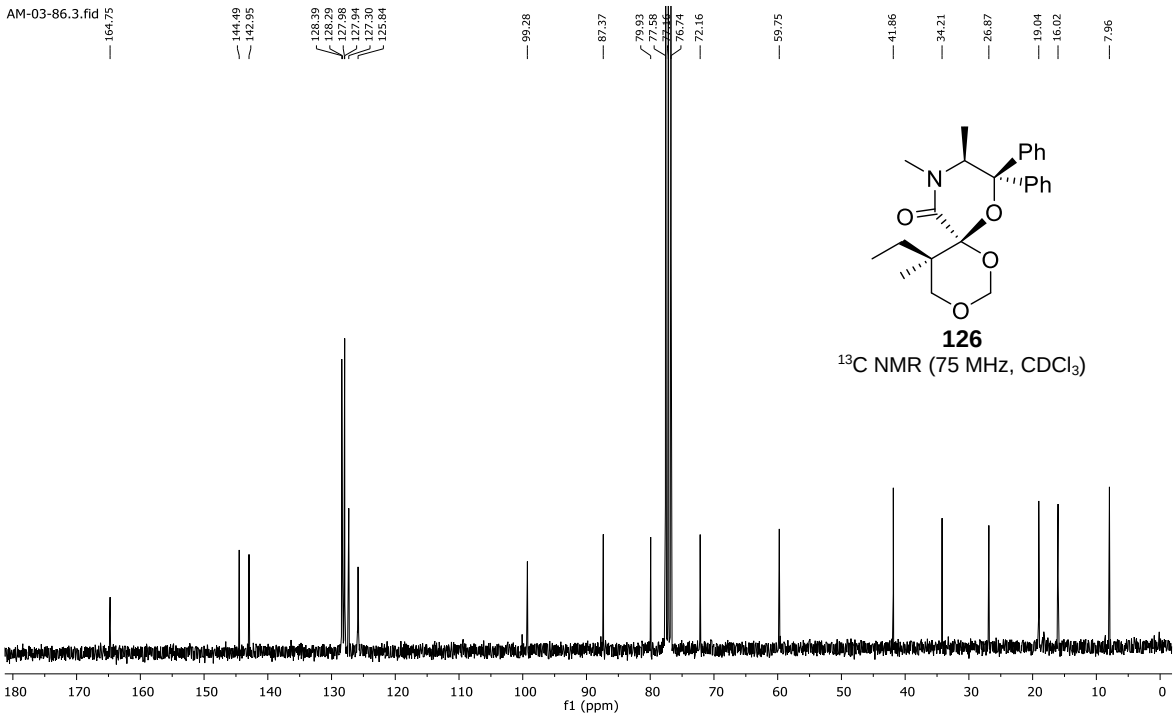
13C NMR (75 MHz, CDCl3)
f1 (ppm)



126

^{1}H NMR (300 MHz, $CDCl_3$)



126

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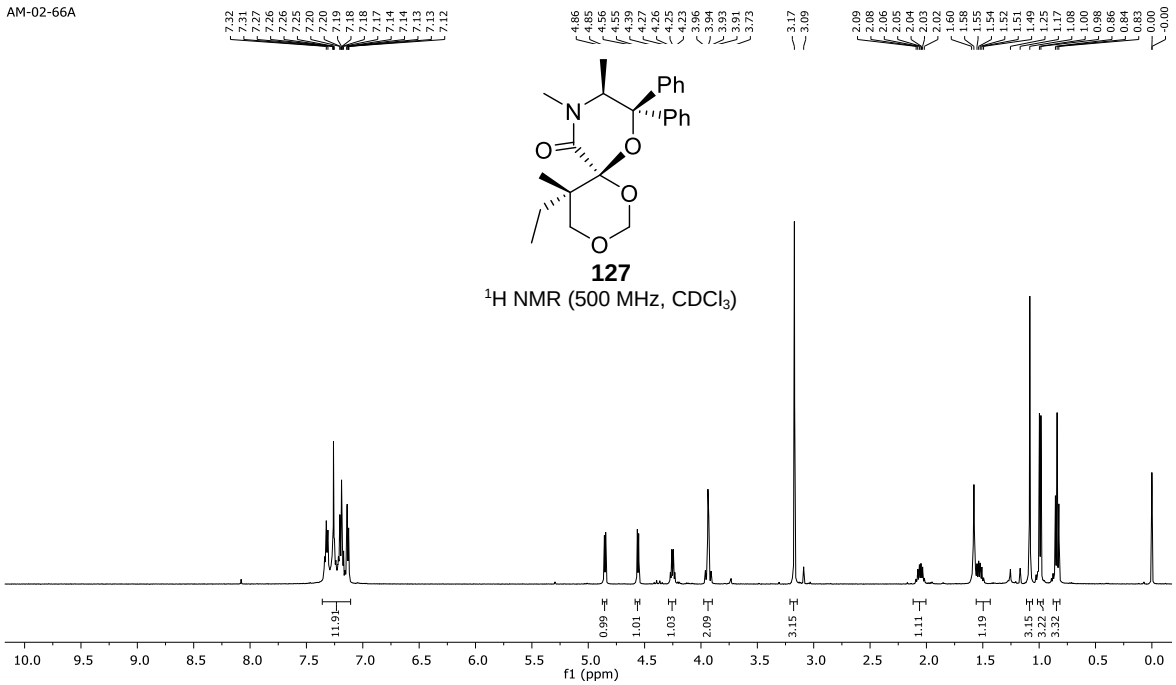

127

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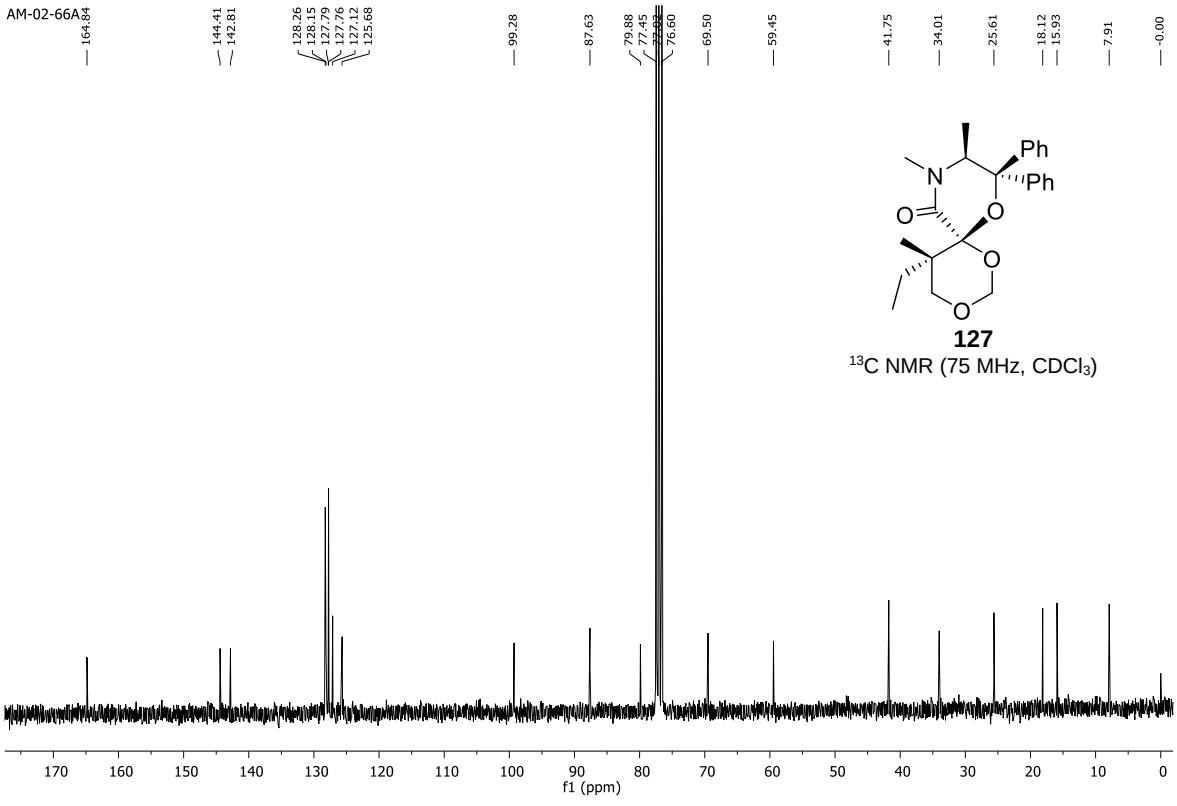
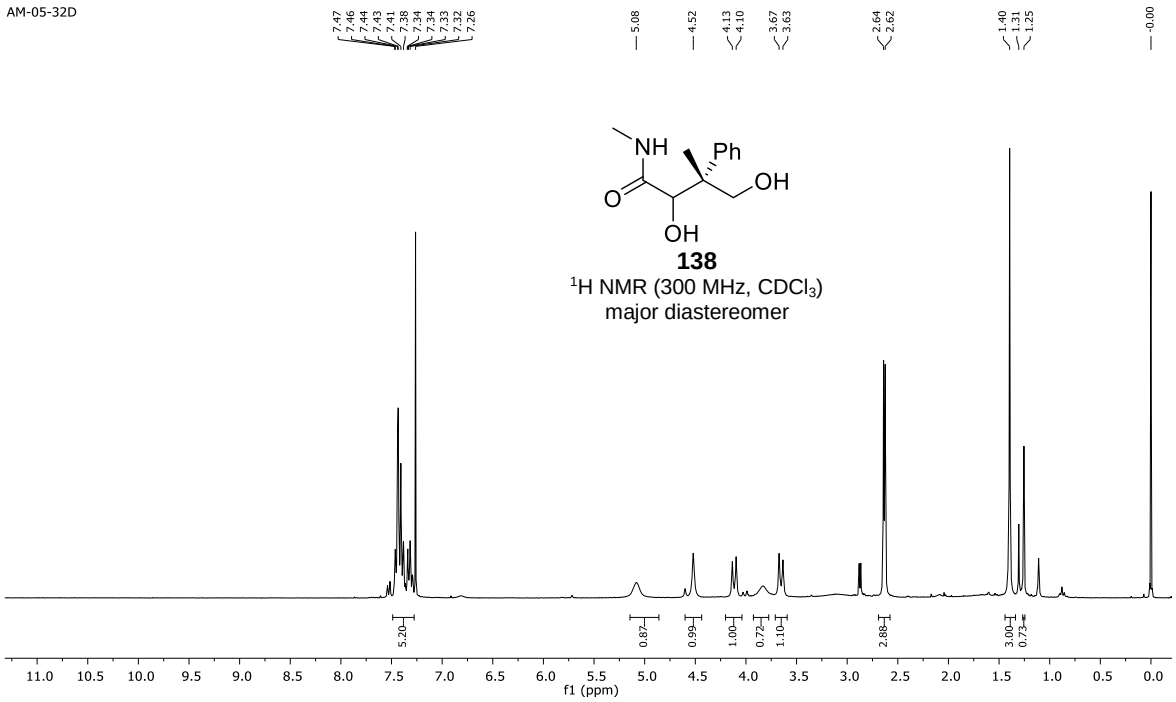


127

^{13}C NMR (75 MHz, $CDCl_3$)


AM-05-32D
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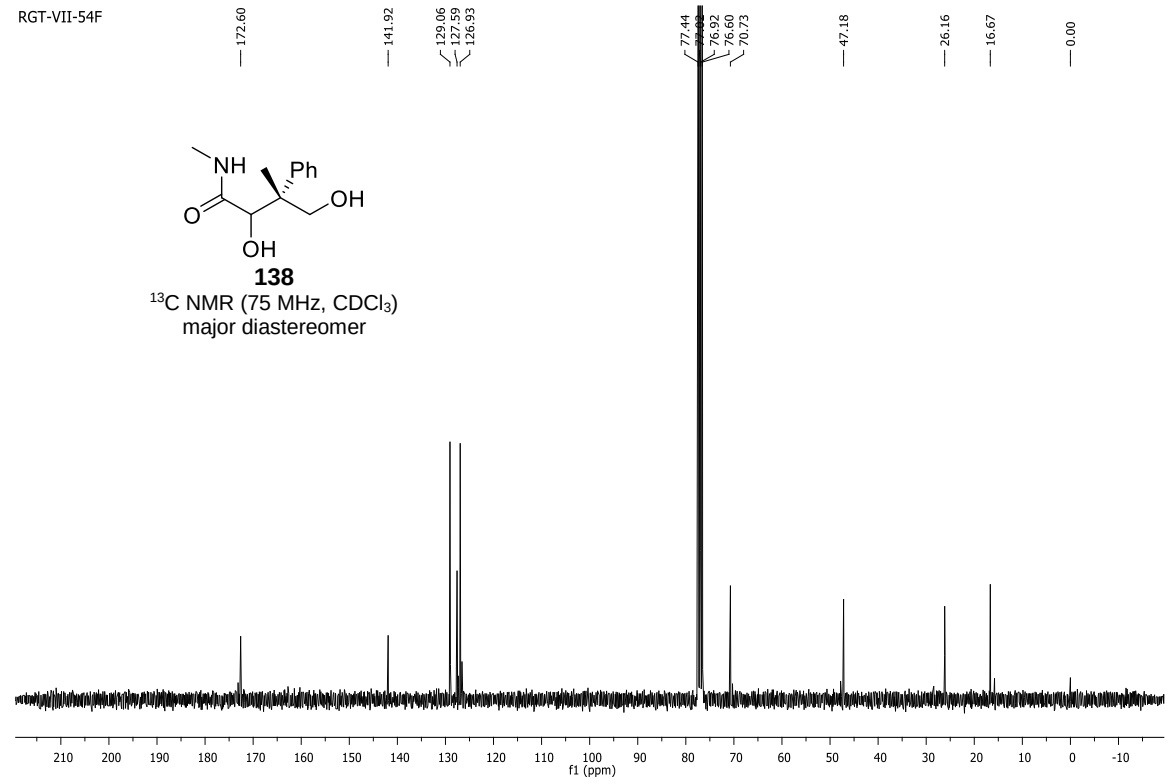
7.46
7.44
7.43
7.41
7.38
7.34
7.34
7.33
7.32
7.26
5.08
4.52
4.13
4.10
3.67
3.63
2.64
2.62
1.40
1.31
1.25
0.00
NH
Ph
OH
O
OH
138
1H NMR (300 MHz, CDCl3)
major diastereomer
5.20
0.87
0.99
1.00
0.72
1.10
2.88
3.00
0.73
f1 (ppm)


RGT-VII-54F
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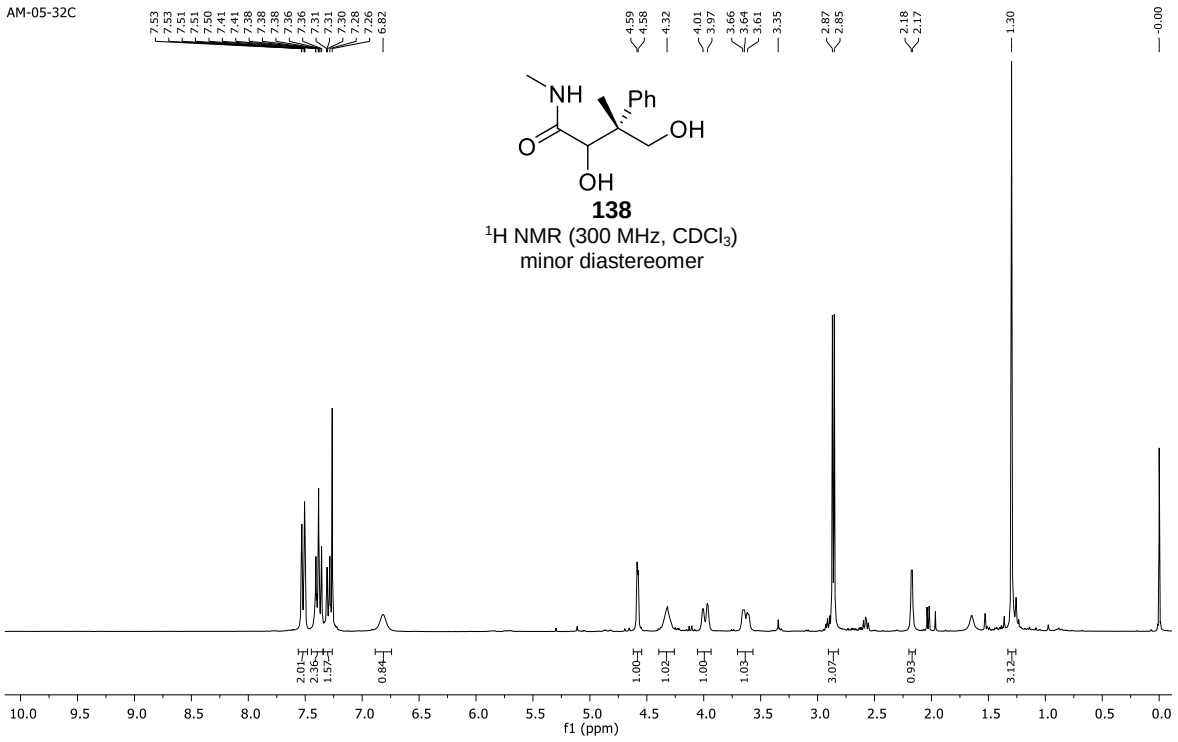
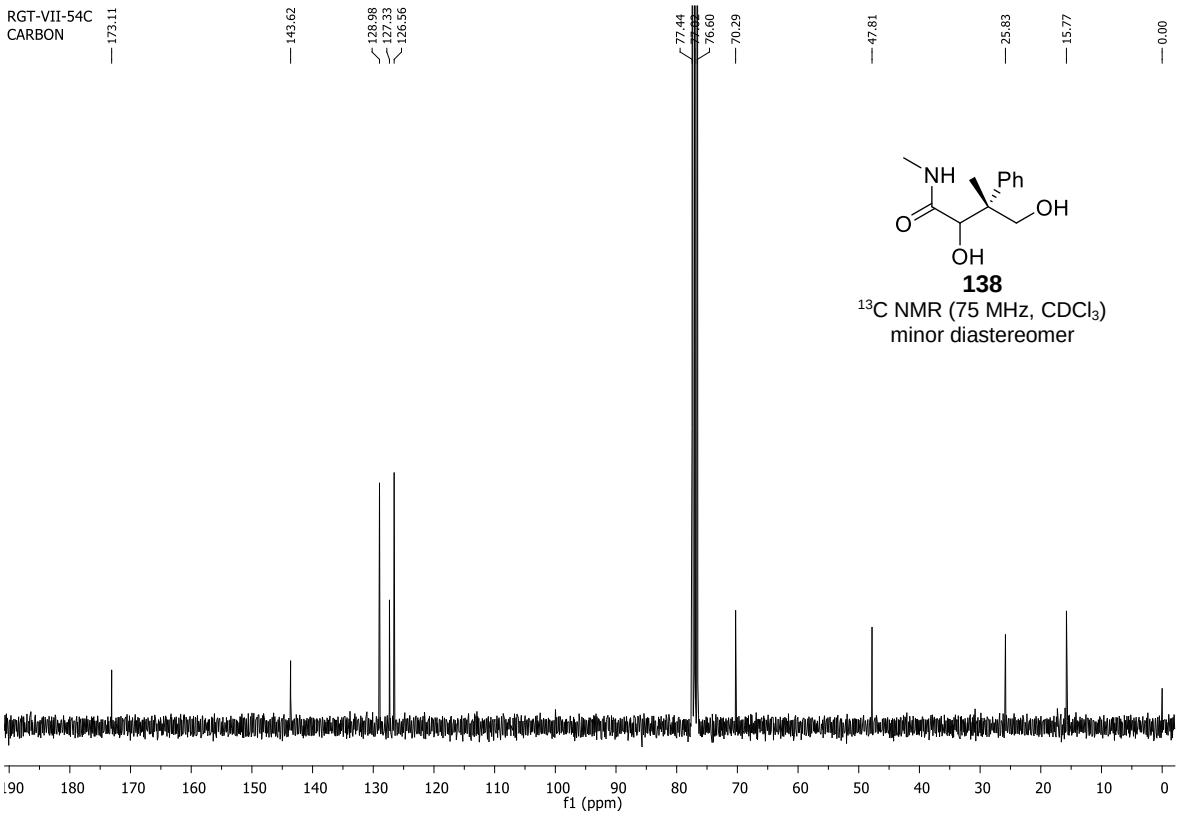
141.92
129.06
127.59
126.93
77.44
76.92
76.60
70.73
47.18
26.16
16.67
0.00
NH
Ph
OH
O
OH
138
13C NMR (75 MHz, CDCl3)
major diastereomer
f1 (ppm)



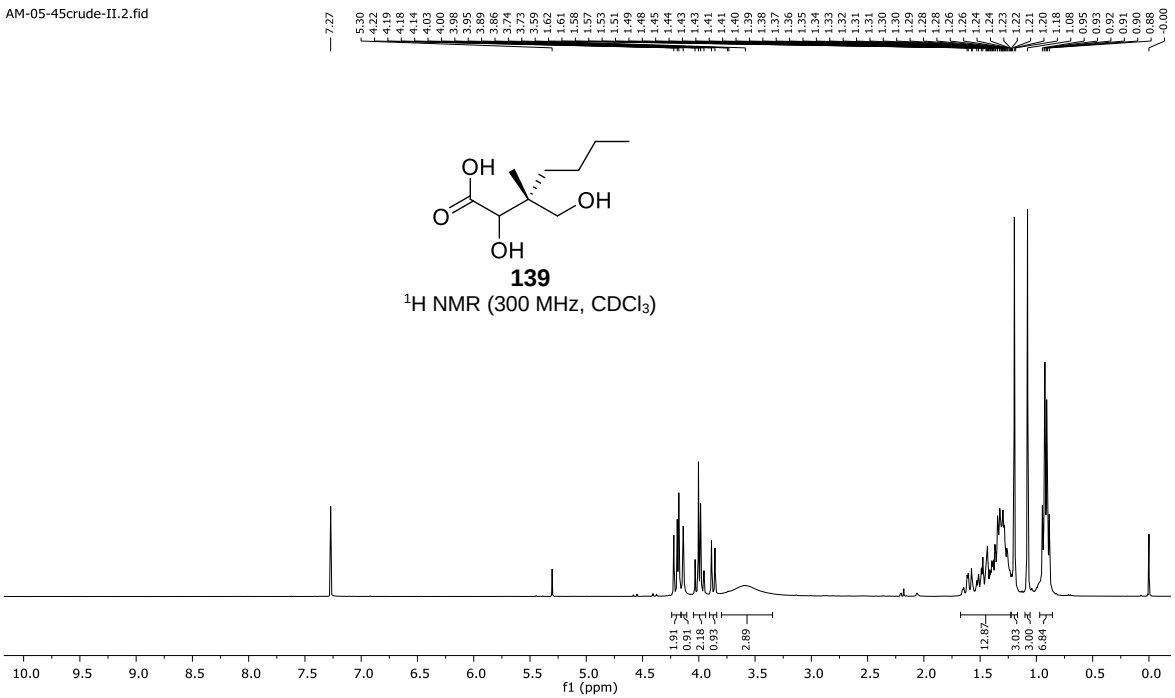
138

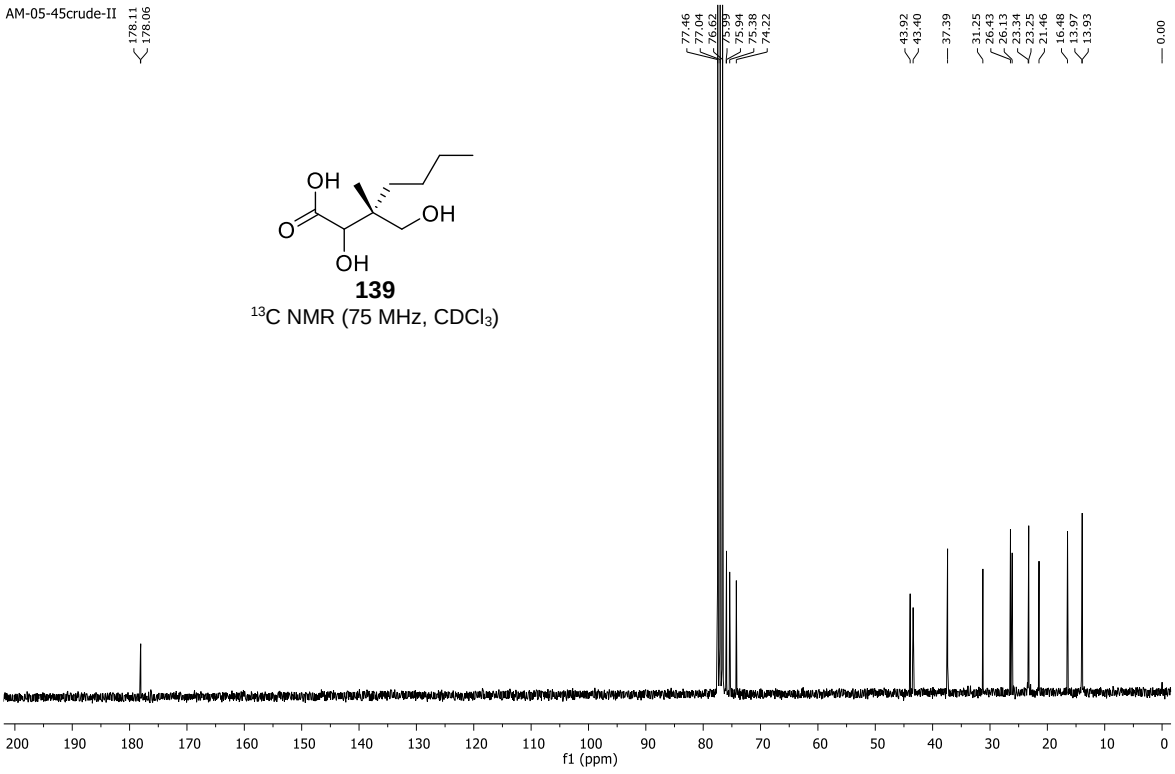
^{1}H NMR (300 MHz, $CDCl_3$)
minor diastereomer

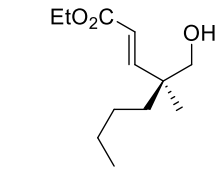


138

^{13}C NMR (75 MHz, $CDCl_3$)
minor diastereomer

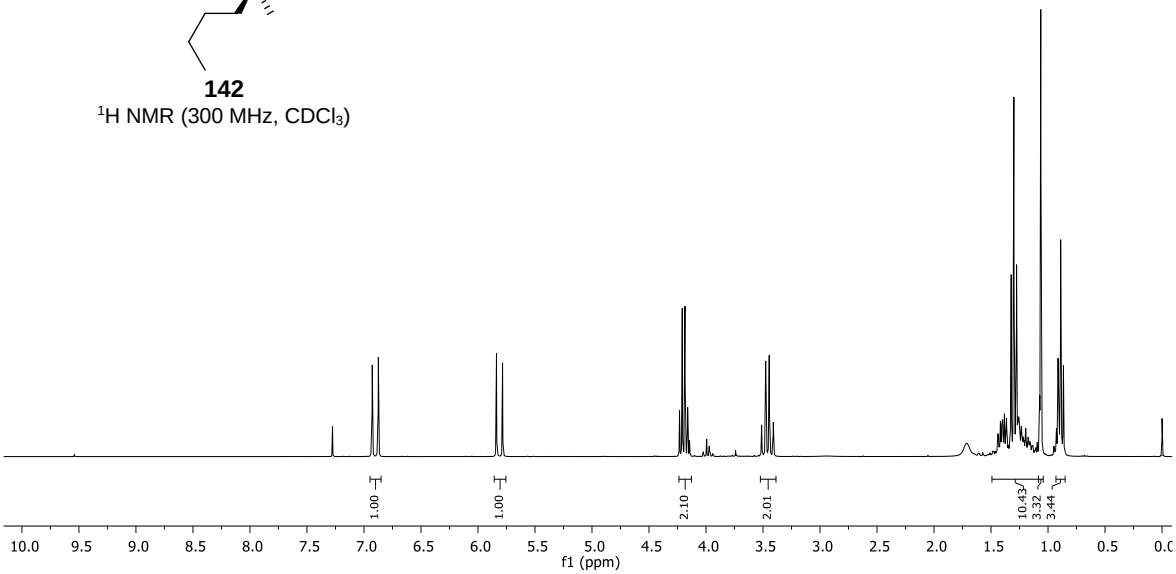

AM-05-45crude-II.2.fid
OH
O
OH
OH
139
1H NMR (300 MHz, CDCl3)
f1 (ppm)

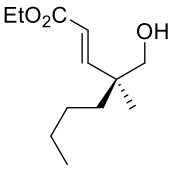

AM-05-45crude-II
OH
O
OH
OH
139
13C NMR (75 MHz, CDCl3)
f1 (ppm)



142

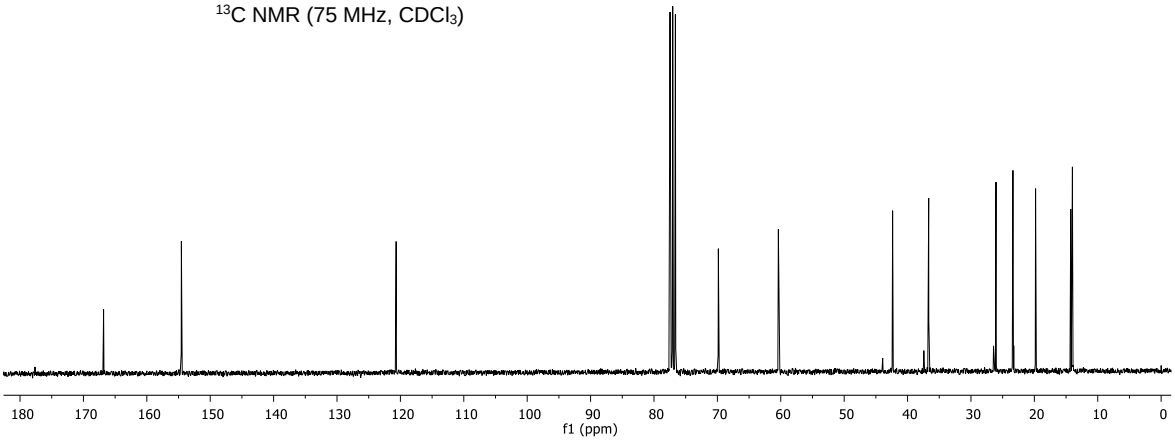
^{1}H NMR (300 MHz, $CDCl_3$)

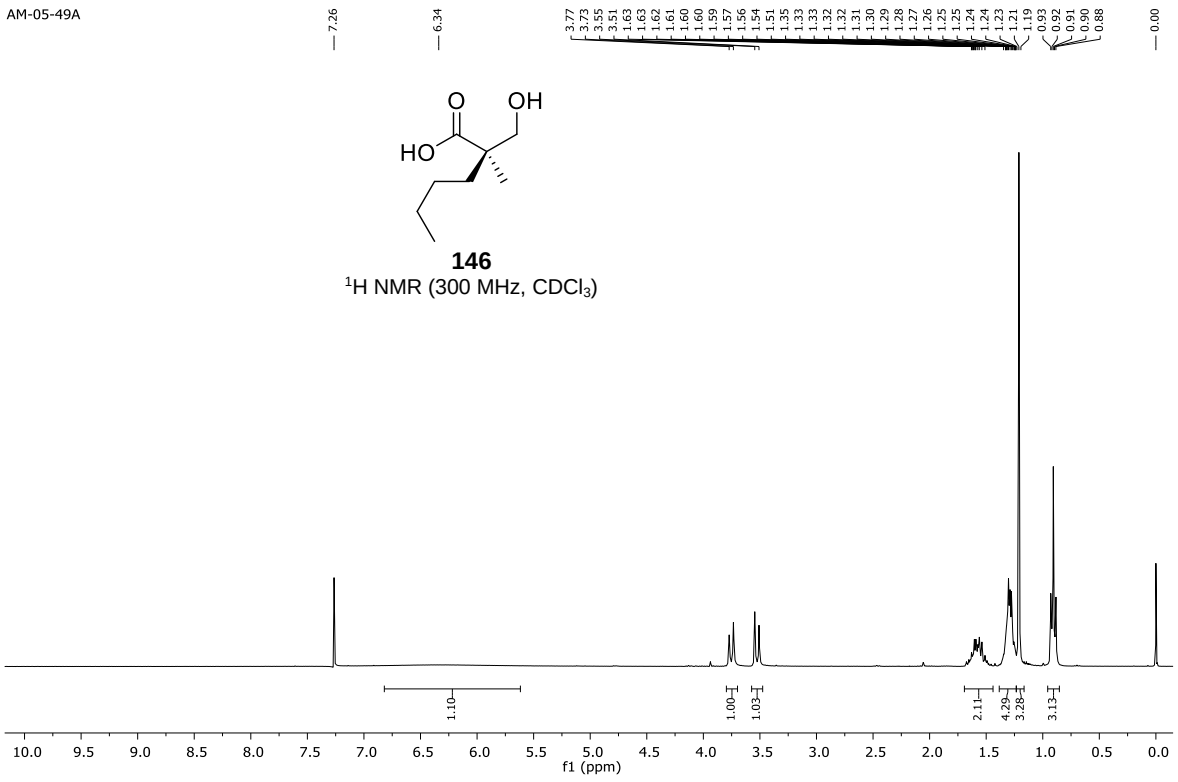




142

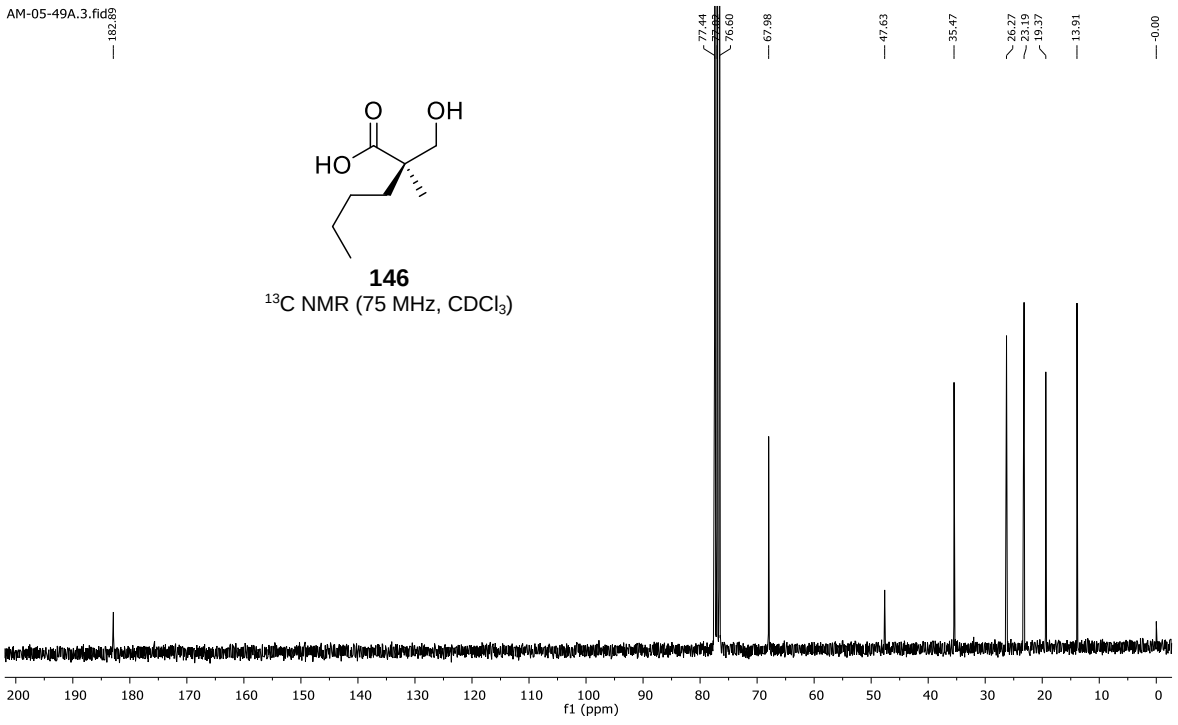
^{13}C NMR (75 MHz, $CDCl_3$)





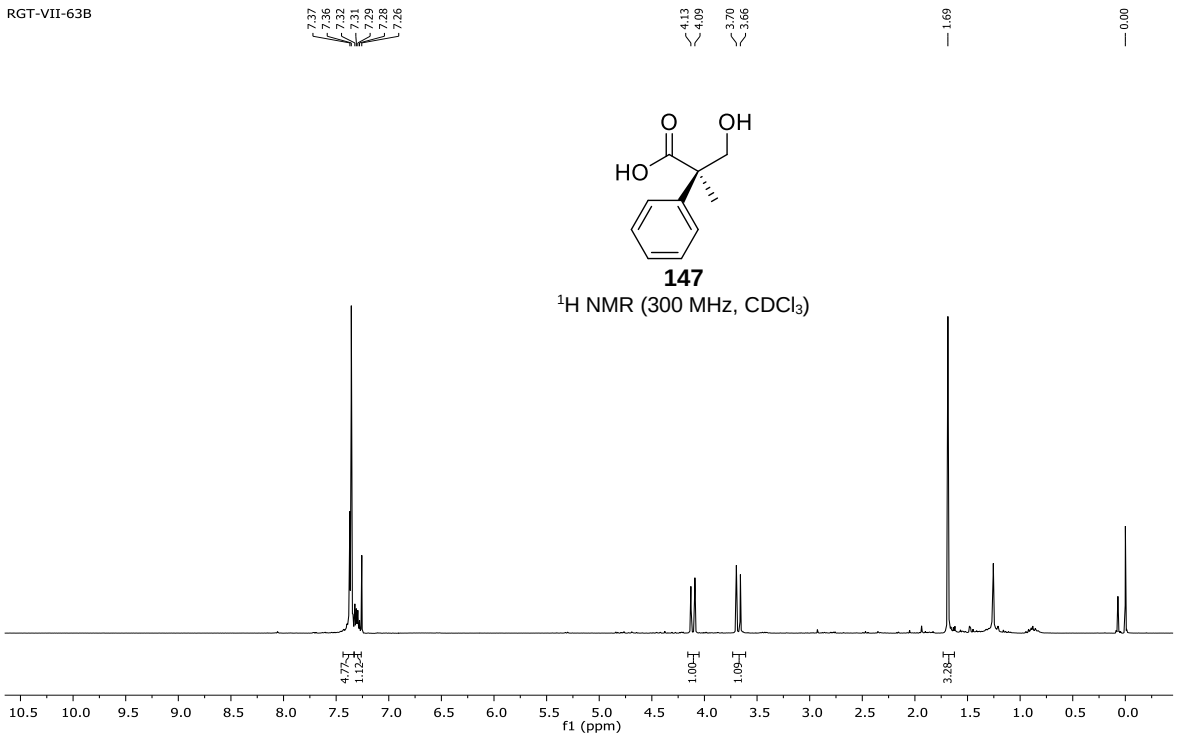
146

^{1}H NMR (300 MHz, $CDCl_3$)



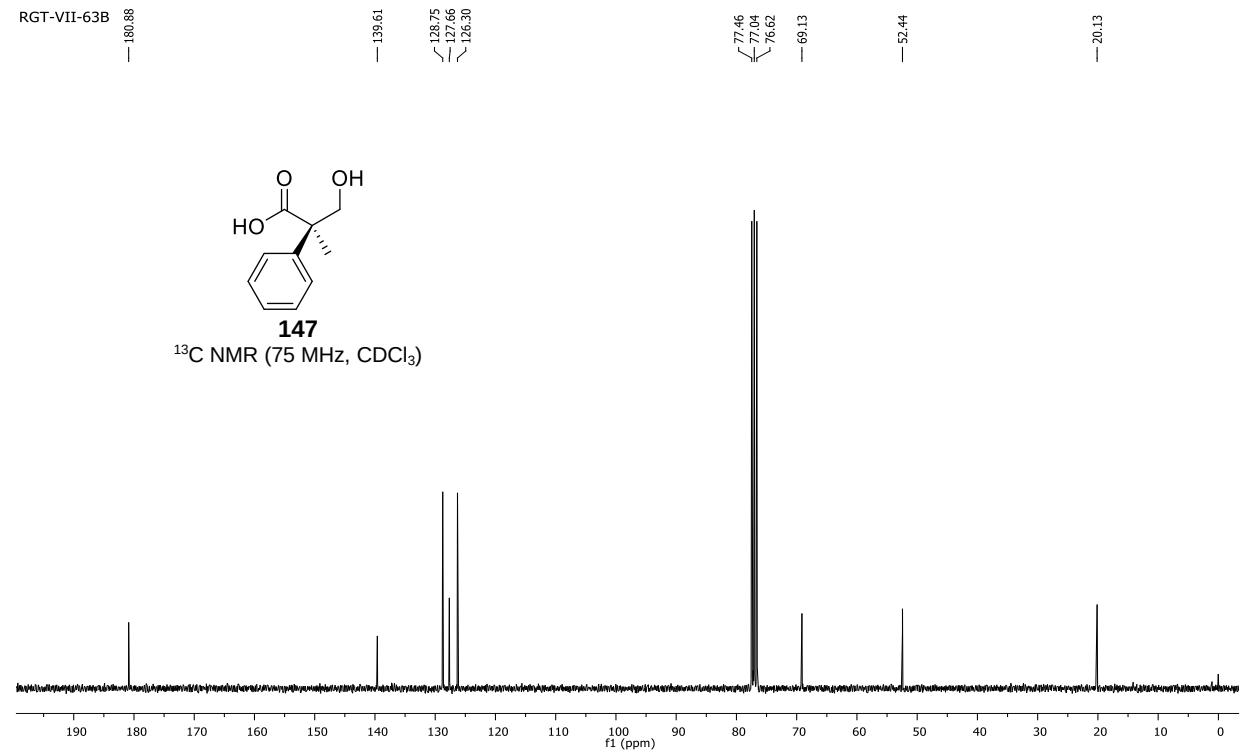
146

^{13}C NMR (75 MHz, $CDCl_3$)



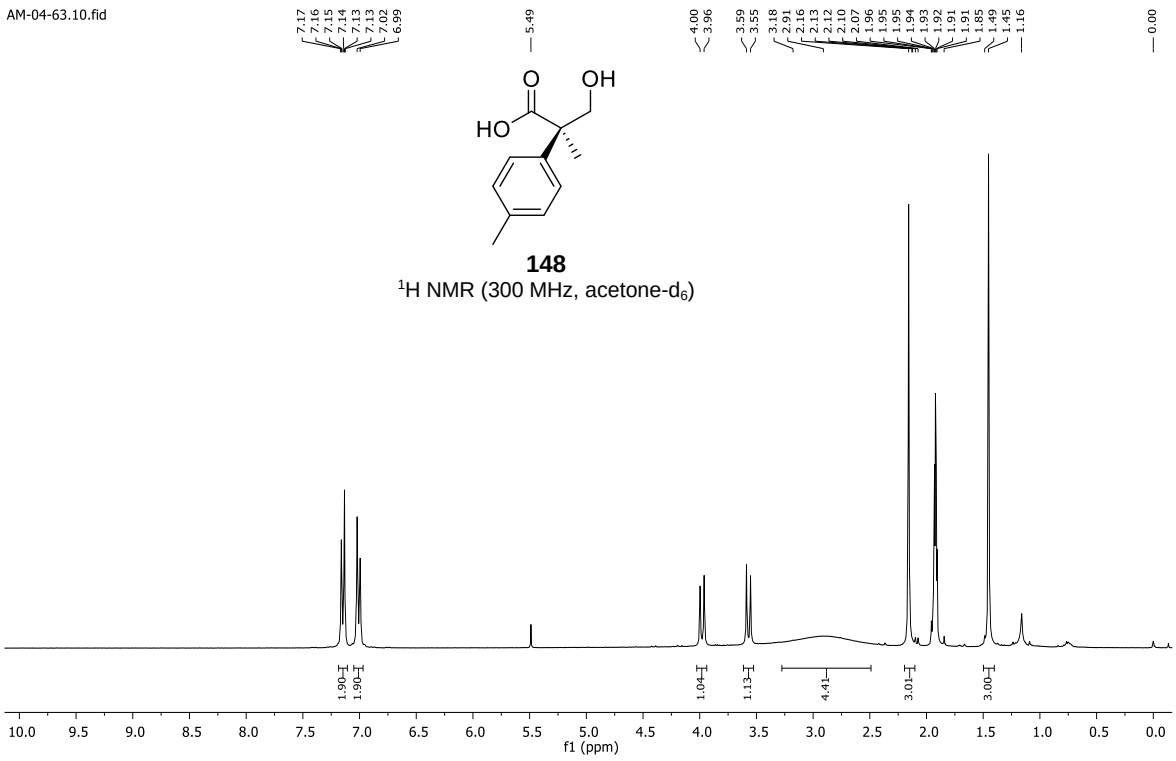
147

^{1}H NMR (300 MHz, $CDCl_3$)



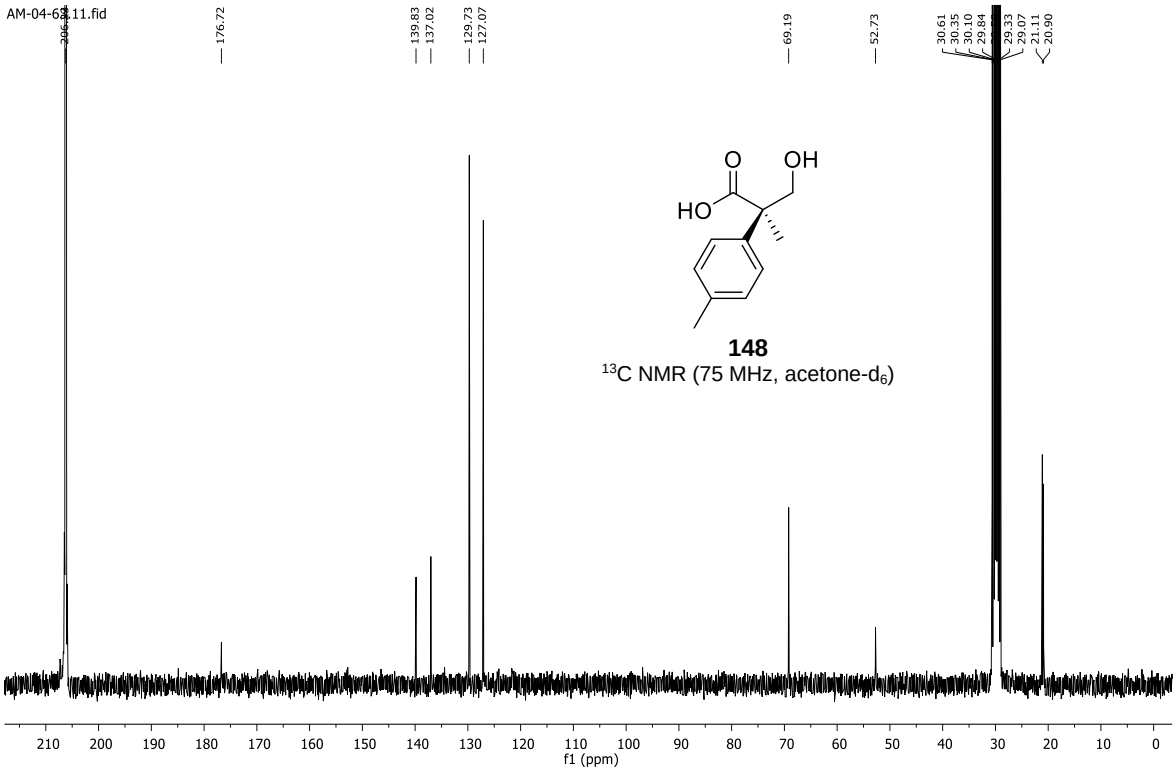
147

^{13}C NMR (75 MHz, $CDCl_3$)



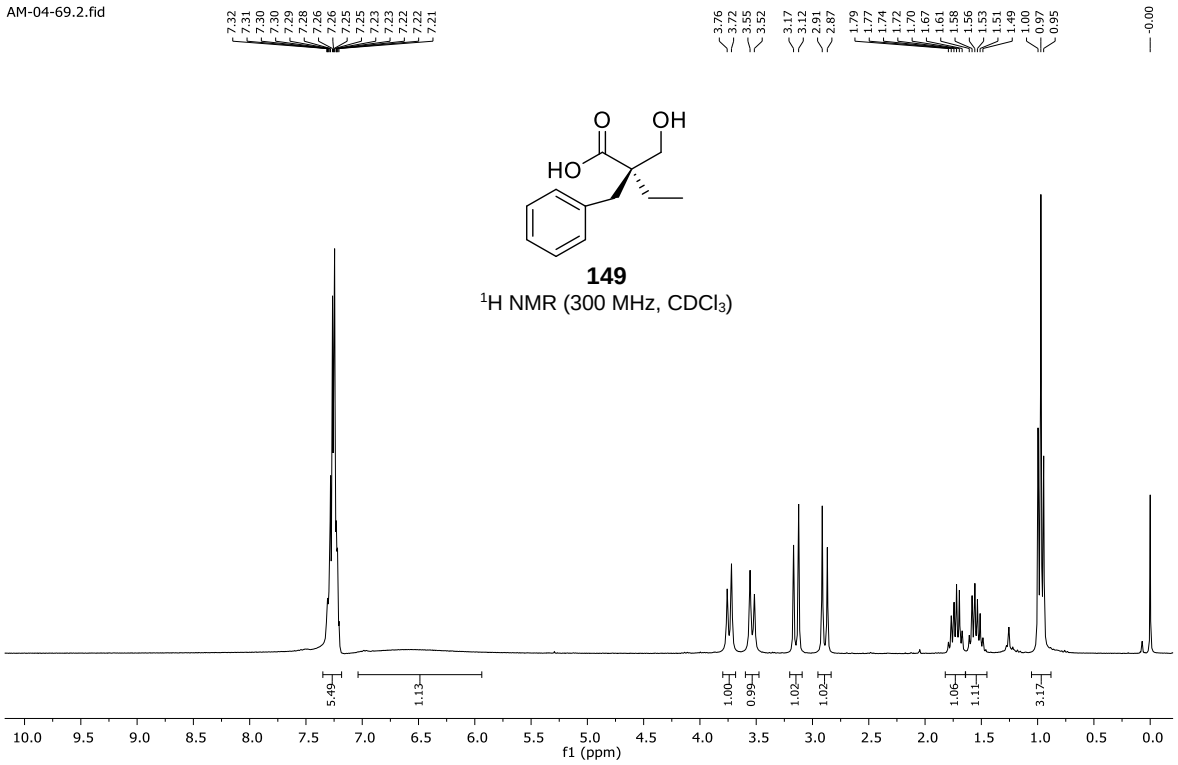
148

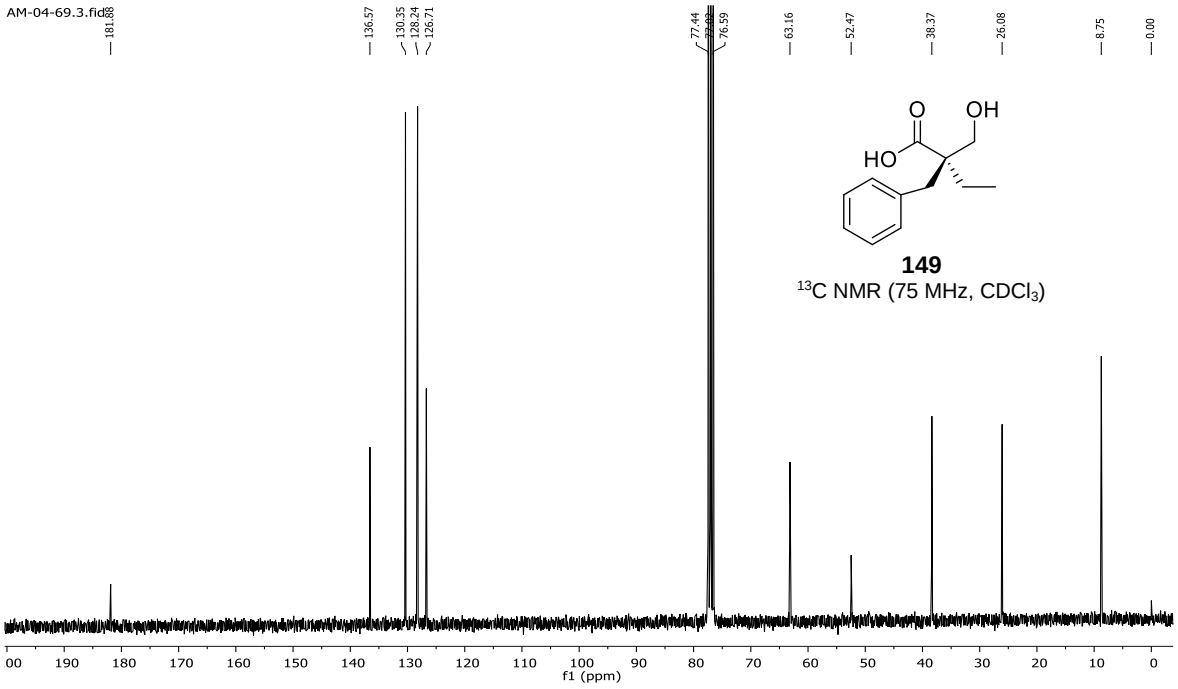
^{1}H NMR (300 MHz, acetone-d_6)



148

^{13}C NMR (75 MHz, acetone-d_6)


AM-04-69.2.fid
7.32 7.31 7.30 7.30 7.29 7.28 7.26 7.26 7.25 7.25 7.23 7.22 7.22 7.21
3.76 3.72 3.55 3.52 3.17 3.12 2.91 2.87 1.79 1.77 1.74 1.72 1.70 1.67 1.61 1.58 1.56 1.53 1.51 1.49 1.00 0.97 0.95 -0.00
O OH HO
149
1H NMR (300 MHz, CDCl3)
5.49 1.13 1.00 0.99 1.02 1.02 1.06 1.11 3.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


AM-04-69.3.fid
181.88 136.57 130.35 128.24 126.71 77.44 77.03 76.59 63.16 52.47 38.37 26.08 8.75 0.00
O OH HO
149
13C NMR (75 MHz, CDCl3)
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Chapter 2

Organocatalytic Asymmetric Michael Addition Reactions of 3-Alkyl/Aryl Tetronic Acids for the Construction of Functionalized Quaternary Stereocenters

2.1 Introduction

Enantiomerically enriched and functionalized quaternary stereocenter-containing furan-2,4(3*H*,5*H*)-diones are important building blocks in organic synthesis and functionalized furan-2,4-diones are used as intermediates in the syntheses of several natural products and pharmaceuticals.[1] Some examples of natural products with quaternary stereocenters are trisporic acid A (**1**),[2] trisporic acid B (**2**),[2] trisporic acid C (**3**), trisporic acid D (**4**), trisporic acid E (**5**), saudin (**6**),[3] (+)-cassiol (**7**),[4] (–)-cassioside (**8**),[4] fraxinellonone (**9**),[5] fraxinellone (**10**), and isofraxinellone (**11**, Figure 2.1).[1-5] The complex natural product, saudin (**6**), which has hypoglycemic activity,[2] was isolated from the leaves of the plant *Clutia richardiana*. (+)-Cassiol (**7**) and (–)-cassioside (**8**) are obtained from the stem of *Cinnamomum cassia* Blume and show potent antiulcer activity.[4] Fraxinellonone (**9**) was isolated from rutaceae and meliaceae plants and it shows antifeeding and growth-regulating activities against insects.[5]

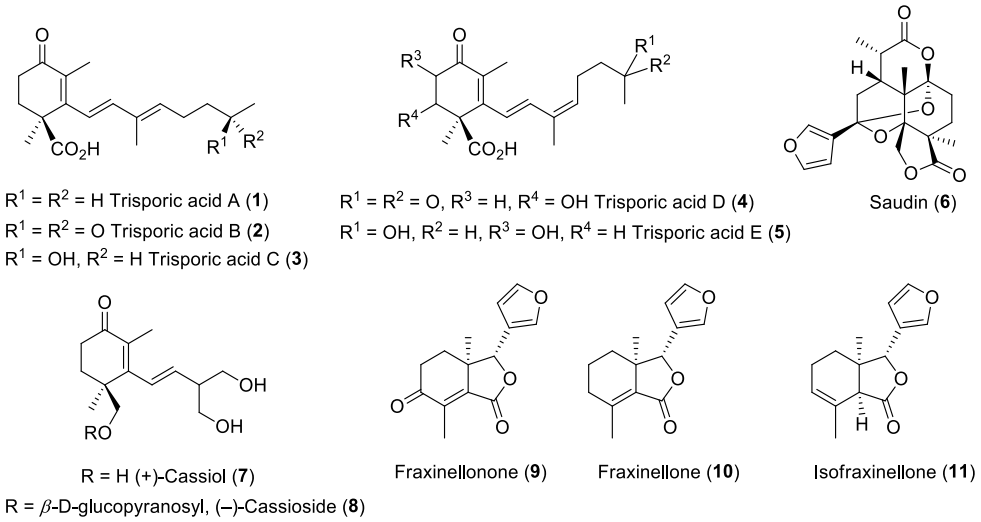


Figure 2.1 Selected quaternary stereocenter-containing natural products.

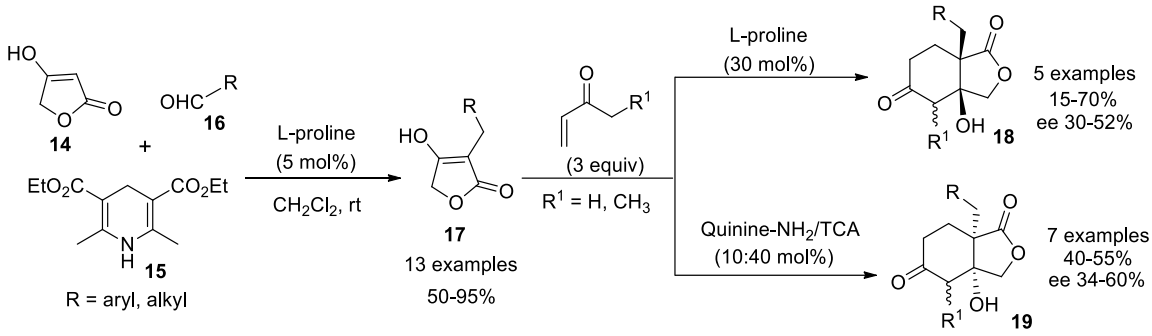
Dihydrofuran-2(3*H*)-ones with vinylogous carboxylic acids are named as tetronic acids **12**. Whereas pyrrolidin-2-ones with vinylogous carboxylic acids are called tetramic acids **13** (Figure 2.2).

Tetronic acid **12** Tetramic acid **13**

Figure 2.2 Generic structures of 3-substituted tetronic and tetramic acids.

2.2 Asymmetric Michael additions of tetronic acids

To the best of our knowledge, there is only one report on the Michael addition of tetronic acids. Recently, Ramachary and coworkers reported[1] the asymmetric cascade Michael-aldol reactions of 3-alkyl tetronic acids **17** with the alkyl vinyl ketones in the presence of L-proline or quinine/TCA (trichloroacetic acid) as catalysts (Scheme 2.1). The first part of this methodology describes the synthesis of a variety of 3-alkyl tetronic acids **17** from tetronic acid (**14**) by the *S*-proline-catalyzed three-component reductive alkylation (TCRA) reaction. The proline-catalyzed reactions of tetronic acid (**14**) with aryl aldehydes or alkyl aldehydes using Hantzsch ester (**15**) as the reducing agent provided the corresponding 3-alkyl tetronic acids **17** in 50-95% yields. Next, asymmetric cascade Michael-aldol reactions of 3-alkyl tetronic acids **17** with alkyl vinyl ketones were investigated using a variety of chiral primary/secondary and cinchona alkaloids as catalysts. From the catalyst survey, *S*-proline and 9-amino-9-deoxyepiquinine/TCA provided moderate enantioselectivities for the corresponding bicyclic lactones **18** and **19** (30-50% ee with *S*-proline and 34-60% ee with quinine/TCA, Scheme 2.1).

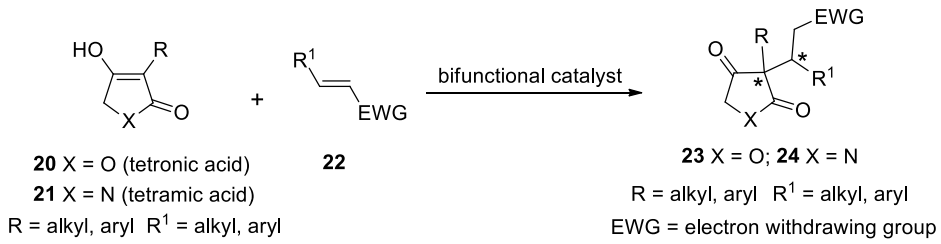


Scheme 2.1 Michael-aldol reaction of 3-alkyl tetronic acids with alkyl vinyl ketones

2.3 Objective

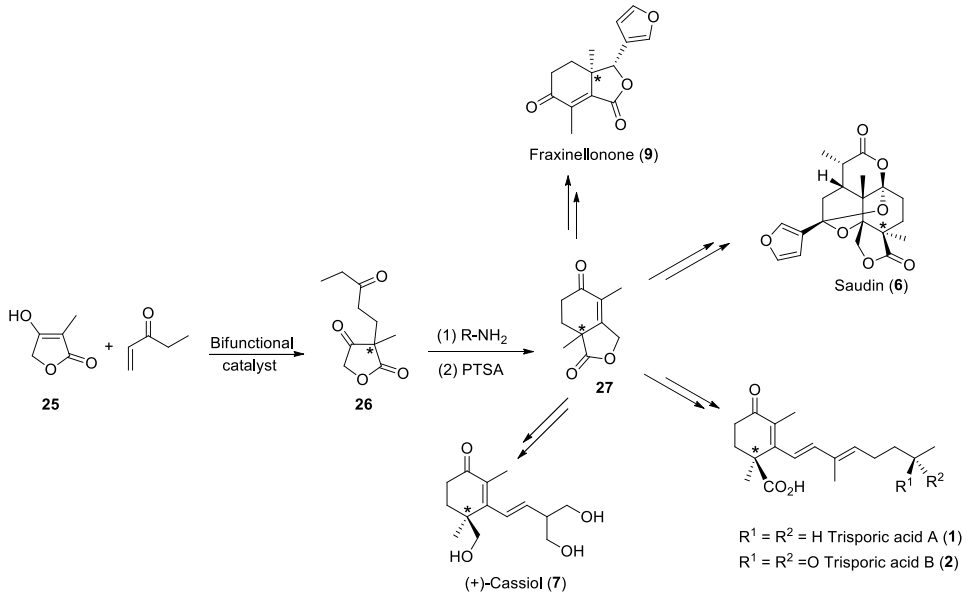
As presented above, a single report[1] has described the use of asymmetric Michael addition reactions of 3-alkyl tetronic acids to obtain functionalized quaternary stereocenter-containing bicyclic-alcohols **18** and **19**. However, this study only reported vinyl ketones as the Michael acceptors and the enantiomeric excess of **18** and **19** is low. Thus, a general method that provides quaternary stereocenter-containing furan-2,4-diones, precursors of bicyclic-alcohols **18** and **19**, with good enantiomeric excess would be useful.

With this objective in mind, the main focus of our studies was the enantioselective synthesis of functionalized quaternary stereocenter containing furan-2,4-diones **23** and pyrrolidine-2,4-diones **24** from 3-alkyl-and/or 3-aryl tetronic acids **20** and 3-alkyl-and/or 3-aryl tetramic acids **21** respectively (Scheme 2.2). Our approach relies on the organocatalytic conjugate additions of a variety of 3-alkyl-and/or 3-aryl tetronic acids **20** or 3-alkyl-and/or 3-aryl tetramic acids **21** to a variety of *α,β*-unsaturated systems **22** (Michael acceptors) in the presence of chiral bifunctional catalysts such as aminothioureas and aminosquaramides (Scheme 2.2).



Scheme 2.2 Strategy for the Michael additions of tetronic or tetramic acids to *α,β*-unsaturated systems.

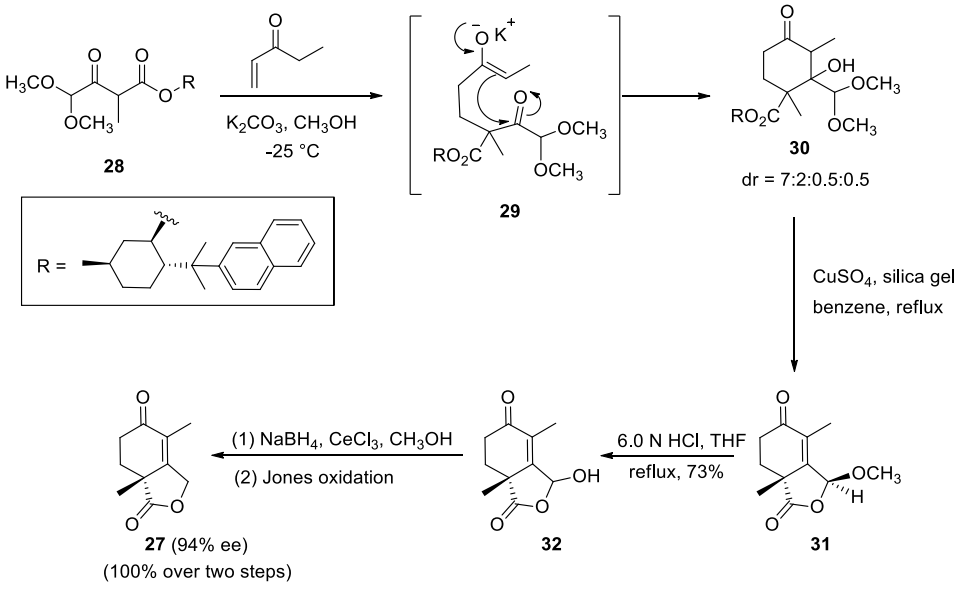
If successful, the Michael adducts obtained from this methodology can be useful intermediates in natural product synthesis. For example, the conversion of Michael adduct **26** to the bicyclic-ketone **27** (Scheme 2.3) is known[1]. White and coworkers[6] first reported the synthesis of **27** (kwon as White's intermediate), which was used as a key intermediate in the synthesis of natural products such as fraxinellonone (**9**), saudin (**6**), trisporic acids A-B (**1**-**2**) and (+)-cassiol (**7**, Scheme 2.3).[1-6] Using our proposed methodology, the key chiral intermediate **27** can be synthesized enantioselectively from **25** (Scheme 2.3).



Scheme 2.3 Our synthetic strategy for the synthesis of White intermediate **27**.

2.3.1 Previous reports on the asymmetric synthesis of the White's intermediate

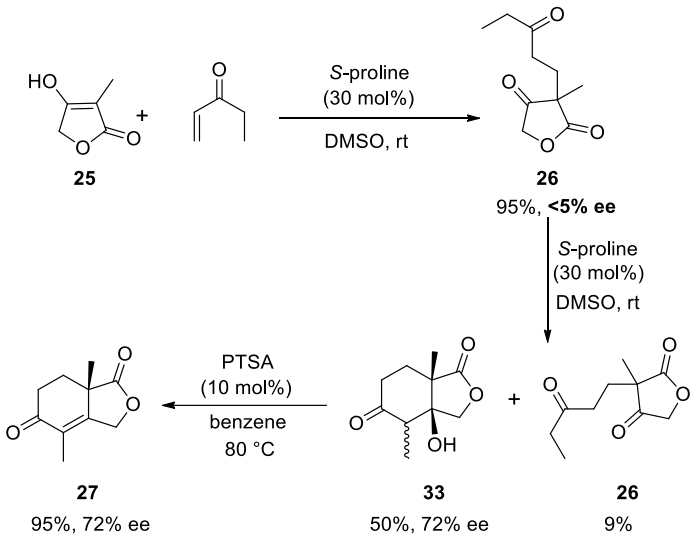
In 1994, Rúveda and coworkers reported[2] the synthesis of key intermediate **27** from **28** *via* a chiral auxiliary-controlled asymmetric Michael addition reaction as the key step (Scheme 2.4). The reaction of **28** with ethyl vinyl ketone provided **30** as mixture of diastereomers (dr = 7:2:0.5:0.5). The diastereomeric adducts **30** were subjected to dehydration in the presence of $CuSO_4$ adsorbed on the silica gel to give **31**, which was then treated with aqueous 6 N HCl to furnish **32** in 73% yield. **32** was transformed into White's intermediate **27** by $NaBH_4$ reduction followed by Jones oxidation of the resulting lactol. (Scheme 2.4).



Scheme 2.4 Synthesis of White's intermediate **27** from **28**

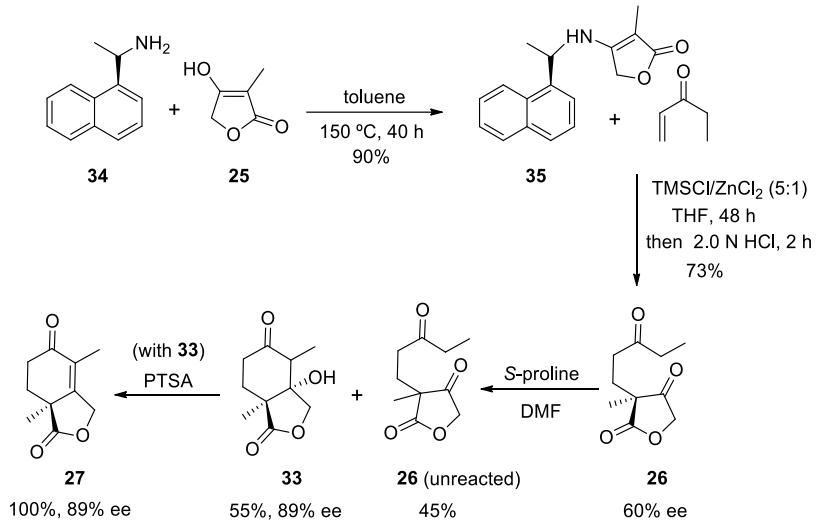
Ramachary and coworkers[1] applied their methodology (Scheme 2.1) in the synthesis of **27** (Scheme 2.5). The *S*-proline-catalyzed reaction of methyl tetronic acid (**25**) with ethyl vinyl ketone afforded **26** in 95% yield with very low enantioselectivity (<5%

ee). The Michael adduct **26** then subjected to a kinetic resolution using *S*-proline as the catalyst (Scheme 2.5) to provide a mixture of bicyclic-alcohol **33** with improved ee (72% ee) and unreacted **26**. Dehydration of **33** furnished bicyclic-ketone **27** with 72% ee (Scheme 2.5).



Scheme 2.5 Synthesis of White's intermediate **27** from **25**

In 2011, Boeckman and coworkers also reported[3d] an asymmetric synthesis of the White intermediate **27**, which was then used as a key starting material in the total synthesis of (–)-saudin (**6**, Scheme 2.6). Chiral primary amine **34** was condensed with methyl tetronic acid (**25**) to give enamine **35**, which was treated with ethyl vinyl ketone (EVK) in the presence of TMSCl/$ZnCl_2$ to give **26** with 60% ee and 73% yield. As in Ramachary's synthesis (Scheme 2.5), a kinetic resolution of **26** was achieved by intramolecular aldol reaction of **26** with *S*-proline to provide a mixture of **33** (55%) with improved enantiomeric excess (89% ee) along with unreacted starting material **26** in 45% yield. Dehydration of **33** gave the key intermediate **27** (Scheme 2.6).



Scheme 2.6 Synthesis of White's intermediate using chiral amine **34**

As described above (Schemes 2.4-2.6), only three reports are available on the asymmetric synthesis of the White intermediate **27**. The Ramachary and Boeckman approaches (Schemes 2.4 and 2.6) are limited by the low to moderate enantioselectivities for the Michael adducts. Although the enantiomeric excess of the Michael adducts was improved by kinetic resolution, only half of the material can be converted to the product. Furthermore, although Rúveda's auxiliary-controlled synthesis[2] gives **27** with good enantiomeric excess (94% ee, Scheme 2.4), this method requires the use of stoichiometric amounts of 8-β-naphthylmenthol as the chiral auxiliary. Notably, the Boeckman procedure also employs stoichiometric amounts of a chiral amine as the auxiliary. In order to overcome these limitations, it was decided to investigate a general, organocatalytic asymmetric synthesis of functionalized quaternary stereocenter containing furan-2,4-diones.

2.4 Results and Discussion

In initial studies, several classes of chiral bifunctional and primary/secondary amine catalysts have been examined for Michael addition reactions of a variety of 3-alkyl-and/or 3-aryl tetronic acids or 3-alkyl-and/or 3-aryl tetramic acids with *α,β*-unsaturated systems. The chiral catalysts that were examined are: (i) cyclohexanediamine,[7a] stilbenediamine,[7b] cinchonidine,[7c,d] cinchonine[7e,f] and proline-derived thioureas (**36**, **37**, **38**, **39** and **40**), (ii) cyclohexanediamine, stilbenediamine, cinchonidine, cinchonine and (*S*)-(−)-2,2′-diamino-1,1′-binaphthalene (DABN)-derived squaramides (**41**, **42**, **43**, **44** and **45**),[7g-j] (iii) MacMillan's catalysts **46** and **47**, (iv) proline-derived catalysts **48** and **49**, (v) primary amine catalysts **50**, **34** and **55** and (vi) cinchona alkaloids **52-54** (Figure 2.3).

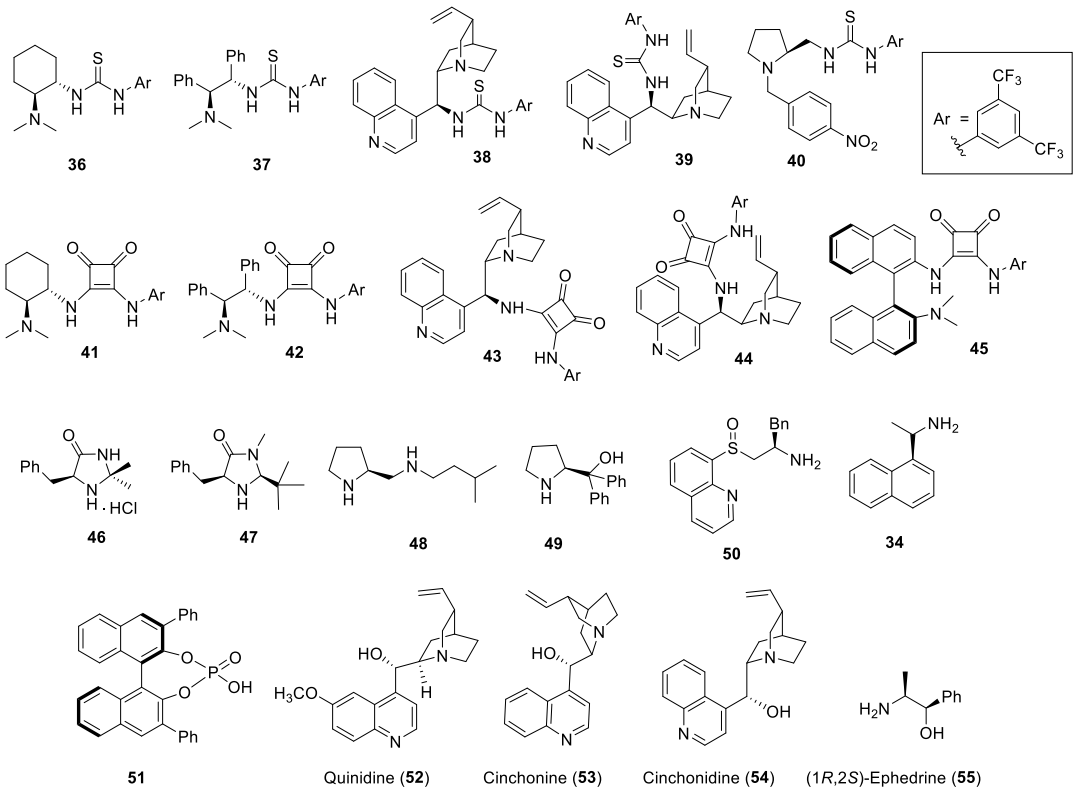
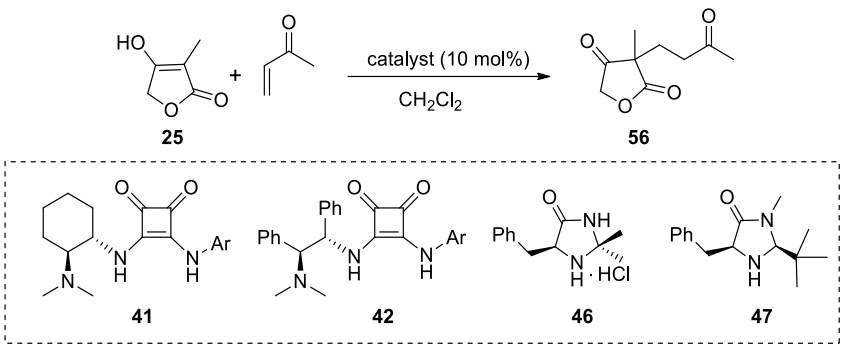


Figure 2.3 Chiral organocatalysts examined for the Michael addition of tetronic acids

Initially, a catalyst survey for the Michael addition reactions of methyl tetronic acid (**25**) with methyl vinyl ketone (MVK) was conducted. Reactions with the aminothiourea catalysts (**36-40**) were feasible. When catalyst **36** was used, the expected product **56** was obtained with 39% ee (36% yield, Table 2.1, entry 1). Reactions of **25** with MVK in the presence of selected aminosquarmide catalysts (**41-44**) provided **56** in 22-88% yields, but with low to moderate enantioselectivities (16-49% ee, Table 2.1, entries 6-9). With catalyst **41**, **56** was obtained with 49% ee (22% yield, Table 2.1, entry 6). Similarly, reactions were conducted with **42** at room temperature as well as at 0 ºC to afford **56** with 33% ee and 47% ee, respectively (Table 2.1, entries 7 and 8). Although cooling the reaction to 0 ºC improved the ee of **56** to 47%, the enantioselectivity decreased to 38% when the reaction was conducted at −15 ºC (Table 2.1, entry 9). This may be due to the low solubility of the catalyst at −15 ºC. Low to moderate enantioselectivities were also obtained with all of the other catalysts, except for **46** and **47** which failed to provide any of the required product. These results are summarized in Table 2.1.

Table 2.1 Catalyst survey for the Michael addition of methyl tetronic acid (**25**) to MVK.

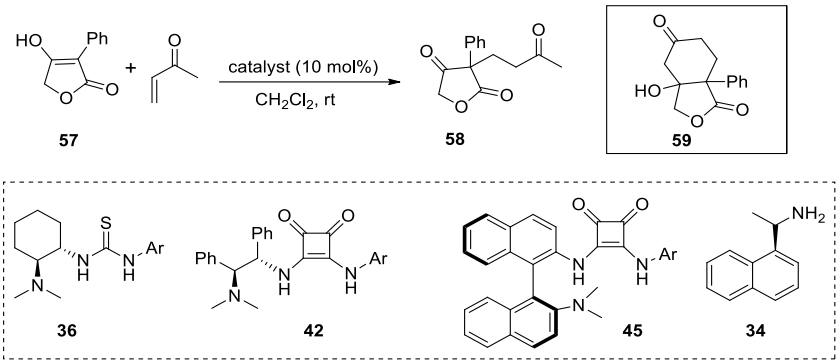


Entry	Catalyst	Time	Temp	Yield (%)[a]	ee (%)[b]
1	**36**	20 h	0 ºC	36	39
2	**37**	185 h	0 ºC	29	33
3	**38**	186 h	0 ºC	62	27
4	**39**	188 h	0 ºC	61	18
5	**40**	206 h	0 ºC	27	18
6	**41**	20 h	0 ºC	22	49
7	**42**	36 h	rt	88	33
8	**42**	6 h	0 ºC	31	47
9	**42**	53 h	-15 ºC	24	38
10	**43**	208 h	0 ºC	62	23
11	**44**	209 h	0 ºC	71	16
12	**46**	240 h	0 ºC	-	-
13	**47**	240 h	0 ºC	-	-
14	**52**	115 h	0 ºC	35	12
15	**53**	115 h	0 ºC	43	10
16	**54**	115 h	0 ºC	43	5
17	**$Sc(OTf)_3$ +*R*-BINOL**	120 h	rt	76	5
18	**48+PTSA**	57 h	rt	26	8
19	**34**	72 h	rt	64	4

[a]isolated yields, [b]chiral HPLC

In related studies, a catalyst survey for the Michael addition reactions of phenyl tetronic acid (**57**) with methyl vinyl ketone (MVK) was also conducted. All of the selected aminothiourea catalysts (**36-40**) were capable of providing the Michael adduct, but with low enantioselectivities (6-16% ee, Table 2.2, entries 1-5). With catalyst **36**, the expected product **58** was obtained in 88% yield, but only 16% ee (Table 2.2, entry 1), which is the best result with aminothiourea catalysts examined in this study. Similarly, reactions were also feasible in the presence of the squaramide catalysts **41-44** (Table 2.2, entry 6-9) but **45** failed to catalyze the reaction. Reactions with catalyst **42** were conducted at room temperature as well as at reflux in CH_2Cl_2 to furnish **58** with 39% ee and 36% ee respectively (Table 2.2, entries 7 and 8). When catalyst **34** was used, the Michael adduct **58** was obtained as the minor product (27%, Table 2.2, entry 17), with **59**, the product of an intramolecular aldol reaction of **58** being the major product (67% yield, 5% ee). Unfortunately, as with the tetronic acid **25**, the reactions of the tetronic acid **57** also provided the Michael adduct **58** in good yield but the enantioselectivities were low to moderate only. These results are summarized in Table 2.2.

Table 2.2 Catalyst survey for the Michael addition of phenyl tetronic acid (**57**) to MVK



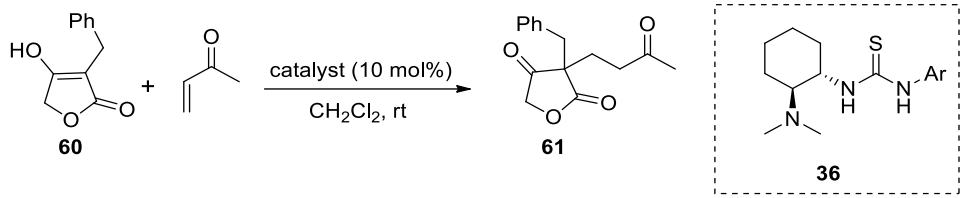
Entry	Catalyst	Time	Yield (%)[a]	ee of 58 (%)[b]
1	**36**	150 h	88	16
2	**37**	151 h	95	14
3	**38**	212 h	76	8
4	**39**	120 h	87	6
5	**40**	152 h	65	11
6	**41**	120 h	13	4
7	**42**	89 h	43	39
8[c]	**42**	30 h	57	36
9	**43**	167 h	67	27
10	**44**	79 h	32	27
11	**45**	168 h	-	-
12[d]	**46**	140 h	90	3
13[d]	**47**	408 h	45	rac
14[d]	**$Sc(OTf)_3$ + 42**	197 h	11	rac
15	**49**	72 h	80	rac
16	**50**	90 h	55	4
17[e]	**34**	20 h	27	rac

[a]isolated yields; [b]chiral HPLC; [c]reaction under reflux; [d]reaction in $CHCl_3$; [e]catalyst **34** gave **58** and **59**

The organocatalytic Michael additions of benzyl tetronic acid (**60**) to methyl vinyl ketone (MVK) were also examined with the aminothioureas (**36-40**), aminosquaramides

(**41-44**) and MacMillan's catalysts (**46** and **47**). With catalyst **36**, the expected product **61** was obtained in 89% yield and 24% ee (Table 2.3, entry 1), which is the best result obtained for **61** in terms of enantioselectivity. Although all of the catalysts examined provided the Michael adduct **61** in excellent yield, the enantioselectivities for these reactions were low. These results are summarized in Table 2.3.

Table 2.3 Catalyst survey for the Michael addition of benzyl tetronic acid (**61**) to MVK.



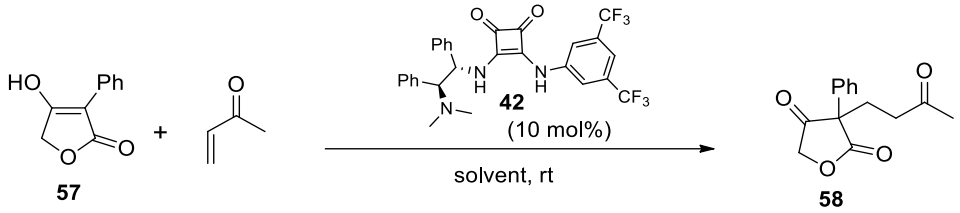
S. No	Catalyst	Time	Yield (%)[c]	ee (%)[d]
1	**36**	195 h	89	24
2	**37**	192 h	89	13
3	**38**	63 h	94	7
4	**39**	149 h	96	5
5	**40**	196 h	95	12
6	**41**	96 h	89	13
7	**42**	96 h	82	19
8[a]	**42**	55 h	35	18
9	**43**	48 h	91	16
10	**44**	124 h	96	11
11[b]	**46**	103 h	29	rac
12[b]	**47**	144 h	26	7

[a]reaction at 0 °C; [b]reaction in $CHCl_3$; [c]isolated yields; [d]chiral HPLC

From the catalyst survey studies (Tables 2.1 to 2.3), it was observed that catalyst **42** afforded good enantioselectivities for **56** (47% ee) and **58** (39% ee) in the conjugate

addition reactions of methyl tetronic acid (**25**) and phenyl tetronic acid (**57**), respectively. Based on these results, a solvent survey was conducted for the Michael addition of phenyl tetronic acid (**57**) to MVK in the presence of catalyst **42** (Table 2.4). The conjugate addition reaction worked in all of the solvents except DMF. Chloroform, dichloromethane and 1,2-dichloroethane emerged as promising solvents in terms of the enantioselectivity of the conjugate addition (Table 2.4, entries 3, 4 and 11). These results are summarized in Table 2.4.

Table 2.4 Solvent survey for the Michael addition of phenyl tetronic acid (**57**) to MVK.

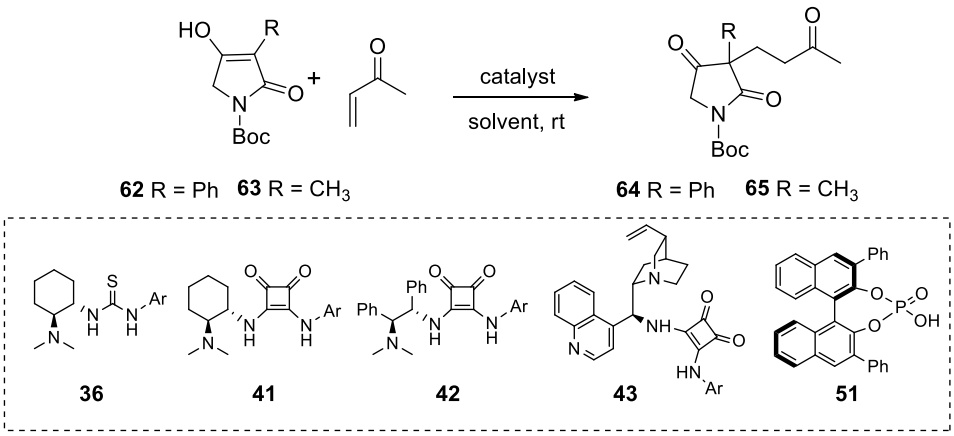


Entry	Solvent	Time	Yield (%)[a]	ee (%)[b]
1	ethyl acetate	140 h	64	24
2	toluene	148 h	31	16
3	$CHCl_3$	162 h	51	32
4	CH_2Cl_2	89 h	43	39
5	THF	167 h	83	5
6	diethylether	174 h	8	19
7	dioxane	168 h	73	22
8	DMF	166 h	61	0
9	CH_3OH	168 h	74	2
10	CH_3CN	169 h	13	9
11	CH_2ClCH_2Cl	265 h	43	32
12	CCl_4	284 h	9	8

[a]isolated yields; [b]chiral HPLC

Since the reactions of tetronic acids proceeded with low to moderate enantioselectivities, it was decided to change the nucleophile to a tetramic acid and, accordingly, a catalyst survey was conducted for the reactions of phenyl tetramic acid (**62**) and methyl tetramic acid (**63**) with MVK (Table 2.5). The aminothiourea **36** and the aminosquaramides **41**, **42** and **43** were screened in the Michael addition. Catalyst **42** provided 27% ee and 26% ee for **62** and **63** respectively (Table 2.5, entries 3 and 9), which are the best results obtained in terms of enantioselectivity for tetramic acids. Chiral phosphoric acid **51** also provided **64** with very low ee (4% ee, Table 2.5, entry 5). Unfortunately, these reactions also provided the Michael adducts in good yields, but with low enantioselectivities. These results are summarized in Table 2.5

Table 2.5 Catalyst survey for the Michael addition of tetramic acids to MVK.



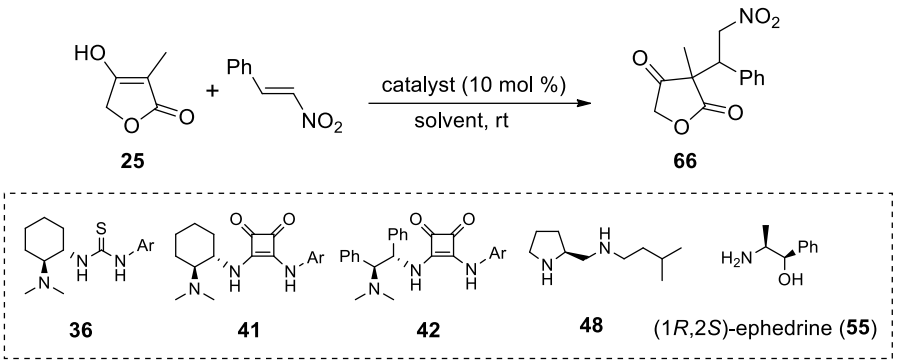
S. No	R	Catalyst	Time	Solvent	Yield (%)[a]	ee (%)[b]
1	Ph	**36**	92 h	CH_2Cl_2	71	rac
2	Ph	**41**	101 h	CH_2Cl_2	75	2
3	Ph	**42**	41 h	CH_2Cl_2	97	27
4	Ph	**43**	92 h	CH_2Cl_2	67	4

5	Ph	**51**	102 h	CH_2Cl_2	36	4
7	Ph	**42**	74 h	toluene	69	7
8	Ph	**42**	76 h	DMF	41	rac
9	CH_3	**42**	27 h	CH_2Cl_2	77	26

[a]isolated yields; [b]chiral HPLC

Since changing the nucleophile from a tetronic acid to a tetramic acid did not improve the enantioselectivity of the Michael addition with MVK, a change in the electrophile was examined next. A catalyst survey was conducted for the reaction of methyl tetronic acid (**25**) with *β*-nitrostyrene. The aminothiourea **36**, the aminosquaramides **41** and **42**, the alkaloids cinchonine (**52**) and quinidine (**53**), the proline-derived diamine (**48**) and ephedrine (**55**) were used as catalysts in this reaction. Unfortunately, all of these catalysts furnished the required product **66** with low diastereoselectivity. Within this selection of catalysts, the best results were obtained with catalysts **42** and **55** (dr = 1.8:1, Table 2.6, entries 3 and 8). These results are summarized in Table 2.6. Since the diastereoselectivity of the reaction was low, the enantiomeric excess of the individual diastereomers was not examined in this study.

Table 2.6 Catalyst survey for the Michael addition of methyl tetronic acid (**25**) to *β*-nitrostyrene.

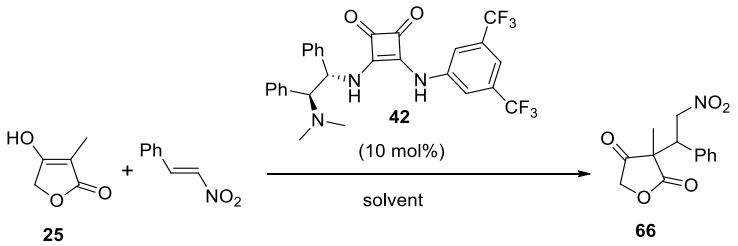


Entry	Catalyst	Time	Solvent	dr[a]	Product 66[c]
1	**36**	100 h	CH_2Cl_2	1.6:1	26
2	**41**	46 h	CH_2Cl_2	1.5:1	36
3	**42**	100 h	CH_2Cl_2	1.8:1	39
4[c]	**42**	50 h	$CHCl_3$	1.5:1	41
5	**48+PTSA**	240 h	DMF	1.6:1	18
6	**52**	46 h	CH_2Cl_2	1.6:1	27
7	**53**	46 h	CH_2Cl_2	1.7:1	31
8	**55**	42 h	CH_2Cl_2	1.8:1	37

[a]^{1}H NMR, [b]isolated yields, [c]5 equivalents of methyl tetronic acid (**25**);

Solvent survey has been conducted for the Michael addition of methyl tetronic acid (**25**) to *β*-nitrostyrene in the presence of catalyst **42**. Unfortunately, as seen from Table 2.7, the reaction is relatively insensitive to a change in the solvent and **66** was obtained in low diastereoselectivity in all of the solvents examined.

Table 2.7 Solvent survey for the Michael addition of methyl tetronic acid (**25**) to β-nitrostyrene.



Entry	Time	Solvent	Temp	dr[a]
1	192 h	DMF	rt	1.5:1
2	240 h	DMF	0 ºC	2.0:1
3	192 h	THF	rt	1.6:1
4	192 h	ethyl acetate	rt	1.5:1
5	192 h	$CHCl_3$	rt	1.8:1
6	192 h	CH_3OH	rt	1.7:1

[a]crude ^{1}H NMR

Further variation of electrophile (Michael acceptor) structure in the conjugate addition reactions of tetronic acids was also examined (Figure 2.4). In these studies, we chose methyl tetronic acid (**25**) and phenyl tetronic acid (**57**) as the nucleophiles, and a range of α, β-unsaturated compounds, **64**–**78,** that differed in the electron withdrawing functional group, as the Michael acceptors. The aminosquaramide **42** was employed as the catalyst in all of these reactions (Figure 2.4).

Only the Michael acceptors **67-72**, which do not have a substituent at the β-position provided the corresponding Michael adducts in good yields. Electrophiles **67-72** afforded corresponding Michael adducts **56**, **58** and **81-86** in good yields with low to moderate

enantioselectivities (Figure 2.4). Reactions with the allyl trichloroacetimidates **73** and **74** provided the corresponding *O*–allylated or *O*-cinnamylated tetronate derivatives instead of the required *C*–alkylation products. The reactions with electrophiles **75-79**, which have a substituent at the β-position, were not successful and only starting materials were recovered. Presumably, in these cases, steric hindrance by the β-substituent in the Michael acceptor prevents C–C bond formation with the nucleophile. Interestingly, the reaction of **57** with **80** afforded only the *Z*-isomer of **86** in 28% yield, but as a racemate.

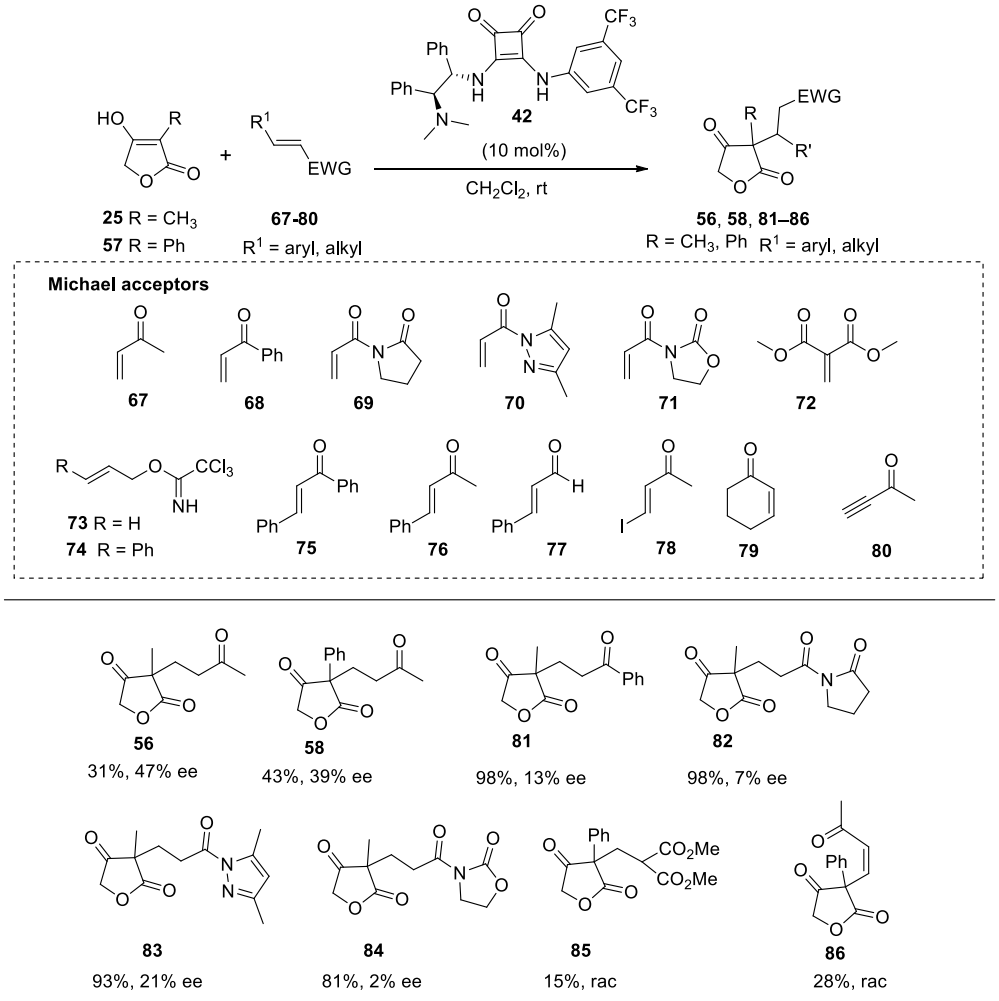
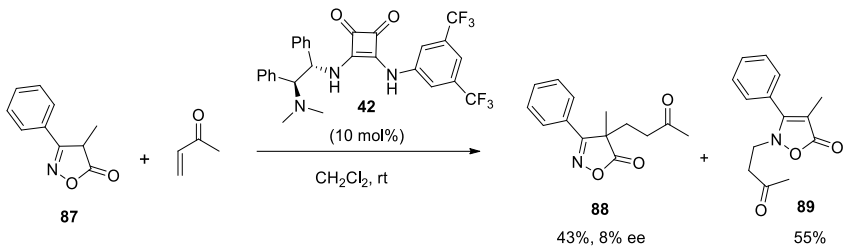


Figure 2.4 Study of various electrophiles in the Michael addition reactions.

A reaction of isoxazol-5(4*H*)-one **87** with MVK was also examined in the presence of catalyst **42**. In this case, a mixture of the product of *C*–alkylation **88** (43% yield, 8% ee) the product of *N*–alkylation **89** (55% yield, Scheme 2.7) was obtained.

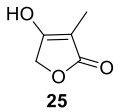
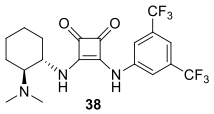
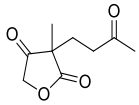
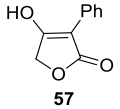
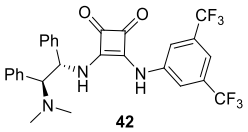
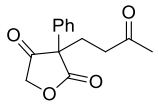
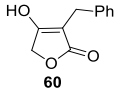
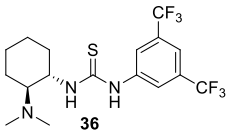
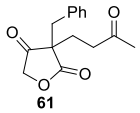
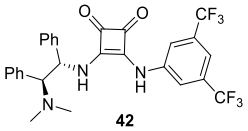
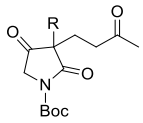


Scheme 2.7

2.4.1 Summary of results

The best results obtained for the Michael addition reactions, in terms of enantioselectivity, are summarized in Table 2.8. Methyl tetronic acid (**25**) afforded **56** with 49% ee using catalyst **38** with MVK (Table 2.8, entry 1). Similarly, phenyl tetronic acid (**57**), phenyl tetramic acid (**62**) and methyl tetramic acid (**63**) with MVK in the presence of catalyst **42** provided the corresponding Michael adducts **58** (39% ee), **64** (27% ee) and **65** (26% ee) respectively (Table 2.8, entry 2 and 4). Catalyst **36** afforded **61** with 24% ee for benzyl tetronic acid (**60**, Table 2.8, entry 3). Among all the electrophiles, MVK in dichloromethane provided better enantioselectivities for the Michael additions as compared with the other electrophiles examined.

Table 2.8 Summary of the best results obtained for the Michael addition reactions of tetronic and tetramic acids.

Entry[a]	Nucleophile	Electrophile	Catalyst	Product	ee(%)
1	 **25**		 **38**	 **56**	49
2	 **57**		 **42**	 **58**	39
3	 **60**		 **36**	 **61**	24
4	 **62** R = Ph **63** R = CH_3		 **42**	 **64** R = Ph **65** R = CH_3	27 (**64**) 26 (**65**)

[a]Reactions were conducted in dichloromethane

2.4.2 Stereochemical model for the Michael addition reactions of tetronic and tetramic acids

Two plausible transition state assemblies can be considered for the Michael addition reactions of 3-alkyl/aryl tetronic acids to MVK (Figure 2.5) in which the carbonyl group of the electrophile is hydrogen-bonded[8] with the squaramide[7g-j] functionality and the deprotonated nucleophile is associated with the ammonium group in the catalyst by ionic interaction. In the transition state assembly I, the electrophile (MVK) adds to the *Si*-face of the tetronic acid to give the *'S'* enantiomer of **90**, whereas in assembly II, MVK adds to the *Re*-face of the tetronic acid to provide the *'R'* enantiomer of **90**. Based on the results obtained, it is likely that there is not much steric interaction between the electrophile

(MVK) and the tetronic acid, and the C-3 substituent does not affect the orientation of the tetronic acid in the transition state assembly. Consequently, the difference in energies for I and II is low, which might explain the low enantioselectivities of the Michael additions examined in this study.

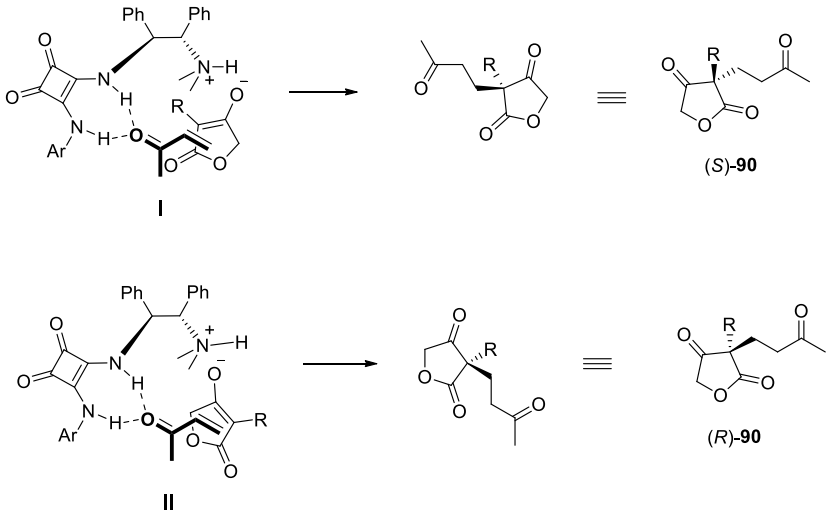


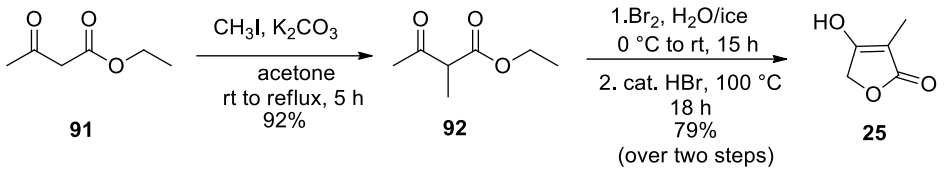
Figure 2.5 Proposed transition states for the Michael addition of 3-alkyl/aryl tetronic acids to MVK.

2.5 Conclusion

In summary, the organocatalytic asymmetric Michael additions of 3-alkyl/aryl tetronic acids or 3-alkyl/aryl tetramic acids to various Michael acceptors for the construction of functionalized quaternary stereocenters were studied. The reactions were feasible with the vast majority of chiral catalysts that were examined, and provided the expected Michael adducts in good yields but with low to moderate enantiomeric excess. Reactions with β-nitrostyrene provided Michael adducts with low diastereomeric excess and reactions with other β-substituted electrophiles were unsuccessful. Structural changes in the Michael acceptor influence the enantioselectivities of the Michael addition, but not significantly. Further optimization of these reactions is required, and these studies are continuing in the Pansare group.

2.6 Experimental Section

4-Hydroxy-3-methylfuran-2(5*H*)-one (25):[9]



To a suspension of K_2CO_3 (2.90 g, 21.1 mmol) in acetone (15 mL) was added ethyl acetoacetate (**91**) (2.44 mL, 19.2 mmol) followed by methyl iodide (1.40 mL, 23.0 mmol) at room temperature. The reaction mixture was then heated to reflux for 5 h. The mixture was cooled to room temperature and the white precipitate was removed by filtration using diethyl ether (30 mL). The filtrates were concentrated to give ethyl 2-methylacetoacetate (**92**), 2.54 g (92%) as colorless liquid. This was used in the next step without purification.

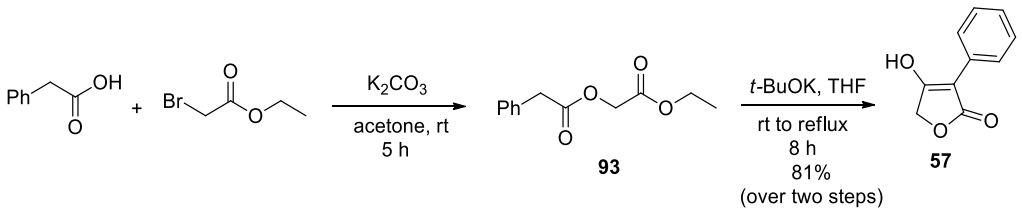
To a mixture of ethyl 2-methylacetoacetate (**92**) (2.00 g, 13.9 mmol) and water (6 mL) was added bromine (0.710 mL, 13.9 mmol) over 5 min at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 15 h. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide the bromoketone, 2.80 g as pale-yellow liquid. This was used in the next step without purification.

To the bromoketone (2.80 g, 12.6 mmol) were added 4 drops of HBr (48% *w/v* in H_2O) at room temperature and the mixture was heated to reflux (100 °C) for 18 h. The mixture was then cooled to room temperature and the precipitate obtained was isolated by

filtration and washed with ethyl acetate. The light brown residue thus obtained is pure methyl tetronic acid (**25**), 1.58 g (51%, over two steps).

R_f = 0.17 (CH_2Cl_2/CH_3OH, 9:1); mp: 183-186 °C; IR (neat): 2959 (br), 2669 (br), 2522 (br), 1722, 1589, 1517, 1443, 1409, 1390, 1345, 1243, 1090, 1029, 911, 846 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 11.83 (brs, 1H, *OH*), 4.56 (q, 2H, *J* = 1.3 Hz, OC*H*$_2$), 1.57 (t, 3H, *J* = 1.3 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.3 (*C*=O or C=*C*OH), 173.0 (*C*=O or C=*C*OH), 94.5 (*C*=COH), 66.6 (O*C*H$_2$), 6.0 (*C*H$_3$).

4-Hydroxy-3-phenylfuran-2(5*H*)-one (57):[10]



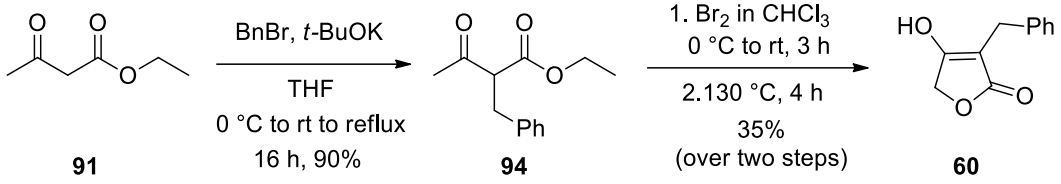
To a solution of phenylacetic acid (3.58 g, 26.3 mmol) in acetone (30 mL) was added anhydrous K_2CO_3 (4.95 g, 35.9 mmol) followed by ethyl bromoacetate (2.64 mL, 24.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 5 h. The mixture was filtered through celite and the residue was washed with EtOAc (20 mL). The filtrates were concentrated under reduced pressure to provide 3.50 g of the diester **93** as a colorless liquid. This was used in the next step without purification.

To a suspension of *t*-BuOK (3.50 g, 39.5 mmol) in dry THF (30 mL) was added the solution of diester **93** (3.50 g 15.7 mmol) in THF (20 mL) over 15 min at room temperature. The reaction mixture was then heated to reflux for 8 h. The mixture was cooled to room temperature and cold water (20 mL) was added. The solvent THF was removed under

reduced pressure and the resulting aqueous suspension was extracted with EtOAc (2 × 10 mL). The aqueous layer was acidified with aqueous 2.0 N HCl (pH~3) and the resulting yellow suspension was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by recrystallization from acetone to provide 1.08 g (81% over two steps) of phenyl tetronic acid **57** as light-yellow crystals.

R_f = 0.34 (EtOAc/hexanes, 3:2); mp: 203-206 °C; IR (neat): 2933 (br), 2579 (br), 1692, 1574, 1460, 1431, 1394, 1351, 1314, 1161, 1059, 1018, 958, 856 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.95-7.88 (m, 2H, Ar*H*), 7.42-7.33 (m, 2H, Ar*H*), 7.26-7.20 (m, 1H, Ar*H*), 4.78 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6):δ 175.0 (*C*=O or C=*C*OH), 172.9 (*C*=O or C=*C*OH), 130.5 (ArC_{ipso}), 128.1 (2 × Ar*C*), 126.3 (3 × Ar*C*), 97.4 (*C*=COH), 66.0 (O*C*H_2).

3-Benzyl-4-hydroxyfuran-2(5*H*)-one (60):[11]



91 **94** **60**

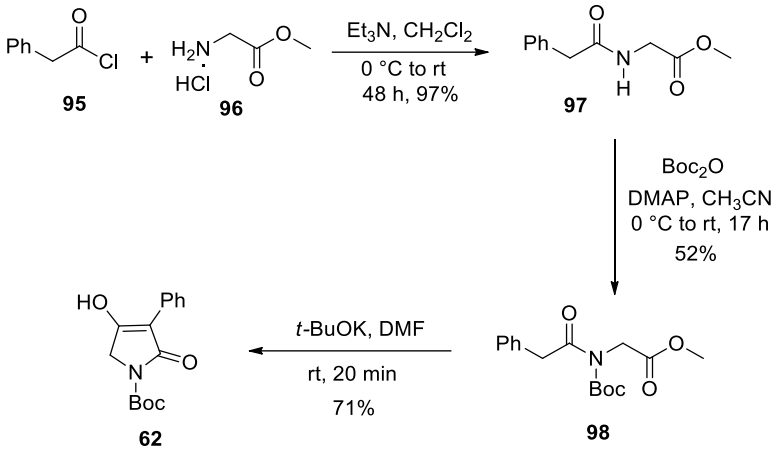
To a suspension of *t*-BuOK (5.11 g, 45.6 mmol) in dry THF (40 mL) was added ethyl acetoacetate (**91**) (5.78 mL, 45.6 mmol) over 5 min at 0 °C, the mixture was stirred for 30 min. and benzyl bromide (4.20 mL, 35.1 mmol) was added dropwise over 10 min at 0 °C. The mixture was warmed to room temperature and heated to reflux for 16 h. The mixture was cooled to room temperature, and then saturated NH_4Cl (30 mL) was added.

The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide 7.52 g (97%) of ethyl 2-benzylacetoacetate (**94**) as a colorless liquid. This was used in the next step without purification.

To a solution of ethyl 2-benzylacetoacetate (**94**) (4.00 g, 18.2 mmol) in $CHCl_3$ (8 mL) was added the solution of bromine (1.03 mL, 20.0 mmol) in $CHCl_3$ (3 mL) over 15 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was concentrated, and the resulting residue was heated at 130 °C for 4 h. The mixture was then cooled to room temperature and the precipitate in the reaction mixture was washed with CH_2Cl_2 (3 × 2 mL). The residue was purified by recrystallization from CH_3OH to provide 1.18 g (35% over two steps) of benzyl tetronic acid (**60**) as a white solid.

R_f = 0.23 (CH_2Cl_2/CH_3OH, 9:1); mp: 153-155 °C; IR (neat): 2970 (br), 2934 (br), 2679 (br), 2644 (br), 2619 (br), 1716, 1585, 1443, 1392, 1360, 1324, 1172, 1097, 1024, 1010, 853 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.08 (brs, 1H, *OH*), 7.30-7.12 (m, 5H, Ar*H*), 4.65 (s, 2H, OCH_2), 3.41 (s, 2H, PhCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.7 (*C*=O or C=*C*OH), 174.0 (*C*=O or C=*C*OH), 139.5 (ArC_{ipso}), 128.2 (2 × Ar*C*), 128.0 (2 × Ar*C*), 125.9 (Ar*C*), 98.4 (*C*=COH), 66.6 (OCH_2), 26.6 (PhCH_2).

***tert*-Butyl 4-hydroxy-2-oxo-3-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (62):**[12]



To a suspension of methyl glycinate hydrochloride (**96**) (4.55 g, 36.3 mmol) in CH_2Cl_2 (40 mL) was added triethylamine (5.76 mL, 39.6 mmol) followed by the dropwise addition of phenylacetyl chloride (**95**) (5.10 g, 33.0 mmol) in CH_2Cl_2 (10 mL) over 30 min at 0°C. The reaction mixture was warmed to room temperature and stirred for 48 h. 1.0 N $NaHCO_3$ (30 mL) was added and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide 6.60 g (97%) of the amide **97** as a light yellow liquid. This was used in the next step without purification.

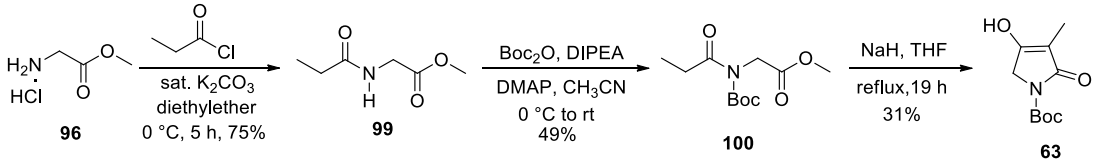
To a solution of **97** (6.60 g, 31.9 mmol) in acetonitrile (60 mL) was added DMAP (194 mg, 1.59 mmol) followed by Boc_2O (8.30 g, 38.2 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 17 h. The mixture was concentrated and cold water (40 mL) was added. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and

concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 9:1) to give 5.10 g (52%) of **98** as light-yellow liquid.

To a solution of **98** (4.10 g, 13.3 mmol) in DMF (40 mL) was added *t*-BuOK (1.80 g, 16.0 mmol) at room temperature. The reaction mixture was stirred for 20 min. Saturated NH_4Cl (40 mL) was added and the mixture was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with water (2 × 20 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by trituration with diethyl ether/ hexane (4:1) to afford 2.60 g (71%) of the pure phenyl tetramic acid (**62**) as a light brown solid.

R_f = 0.17 (CH_2Cl_2/CH_3OH, 9:1); mp: 147-151 °C; IR (neat): 3143 (br), 2998 (br), 2971 (br), 1744, 1717, 1703, 1662, 1638, 1425, 1408, 1349, 1312, 1152, 1102, 1073, 980, 897, 850 cm^{-1}; ^1H NMR(300 MHz, DMSO-d_6): δ 12.38 (br s, 1H, O*H*), 7.88-7.82 (m, 2H, Ar*H*), 7.39-7.30 (m, 2H, Ar*H*), 7.24-7.17 (m, 1H, Ar*H*), 4.27 (s, 2H, OCH_2), 1.48 (s, 9H, OC(CH_3)$_3$); ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.4 (*C*=O or C=*C*OH), 168.0 (*C*=O or C=*C*OH), 149.0 (N*C*OO), 131.1 (ArC_{ipso}), 127.8 (2 × Ar*C*), 127.1 (2 × Ar*C*), 126.2 (Ar*C*), 103.6 (*C*=COH), 81.1 (O-*C*(CH$_3$)$_3$), 47.9 (N*C*H$_2$), 27.8 (O-C(*C*H$_3$)$_3$).

***tert*-Butyl 4-hydroxy-3-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (63):**[13]



To a suspension of methyl glycinate hydrochloride (**96**) (4.50 g, 36.0 mmol) in Et_2O (10 mL) was added a saturated, aqueous solution of K_2CO_3 (19 mL) followed by dropwise addition of propanoyl chloride (4.90 g, 54.0 mmol) over 15 min at 0 °C. The reaction

mixture was stirred for 5 h at 0 °C and cold water (10 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide 3.90 g (75%) of the crude amide **99** as a light-yellow liquid. This was used in the next step without purification.

To a solution of **99** (2.00 g, 13.8 mmol) in acetonitrile (15 mL) were added DMAP (170 mg, 0.140 mmol) and DIPEA (3.60 mL, 20.7 mmol) followed by Boc_2O (3.60 g, 16.5 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 25 h and brine (10 mL) was added. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with cold water (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 9:1) to give 1.36 g (41%) of **100** as light-yellow liquid.

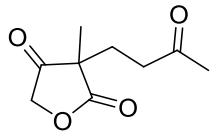
To a refluxing suspension of NaH (244 mg, 6.10 mmol, 60% dispersion in mineral oil) in dry THF (10 mL) was added dropwise a solution of **100** (1.36 g, 5.55 mmol) in THF (2 mL) over 5 min and the reflux was continued for 19 h. The mixture was cooled to room temperature and cold water (10 mL) was added at 0 °C. The solvent THF was removed under reduced pressure and the residue was washed with EtOAc (2 × 10 mL). The aqueous layer was acidified with 2.0 N HCl (pH~3) and the resulting light brown suspension was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude was purified by trituration in CH_2Cl_2/hexane (9/1) to provide 201 mg (31%) of the pure methyl tetramic acid (**63)** as a light-yellow solid.

R_f = 0. 24 (CH_2Cl_2/CH_3OH, 9:1); mp: 122-129 °C; IR (neat): 2978 (br), 2932 (br), 1747, 1698, 1630, 1437, 1408, 1363, 1308, 1243, 1158, 1083, 1000 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.45 (brs, 1H, *OH*), 4.06 (s, 2H, OC*H*$_2$), 1.53 (s, 3H, C*H*$_3$), 1.45 (s, 9H, 3 × C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.0 (*C*=O or C=*C*OH), 167.4 (*C*=O or C=*C*OH), 148.9 (N*C*OO), 100.8 (*C*=COH), 80.7 (O-*C*(CH_3)$_3$), 48.1 (N*C*H$_2$), 27.8 (O-C(*C*H$_3$)$_3$), 5.9 (*C*H$_3$).

General procedure for the catalytic Michael addition of tetronic or tetramic acids

To a suspension of the tetronic or tetramic acid and the Michael acceptor in dichloromethane was added catalyst (10 mol%) at room temperature or 0 ºC. The reaction mixture was stirred until complete consumption (TLC) of the tetronic or tetramic acid and then concentrated. The residue was purified by flash chromatography on silica gel.

3-Methyl-3-(3-oxobutyl)furan-2,4(3*H*,5*H*)-dione (56):[1]



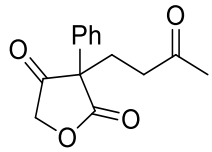
Best ee experiment: The reaction of methyl tetronic acid (**25**) (163 mg, 1.43 mmol), methyl vinyl ketone (58 µL, 0.71 mmol), catalyst **38** (32 mg, 7.1 x 10^{-2} mmol) in dichloromethane (2 mL) at 0 ºC for 20 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 29 mg

(22%) of **56** as a colorless liquid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 23.66 min; t_{major} = 28.15 min; 49% ee.

Best yield experiment: The reaction of methyl tetronic acid (**25**) (146 mg, 1.28 mmol), methyl vinyl ketone (68 µL, 0.86 mmol), catalyst **42** (46 mg, 8.6×10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 36 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 139 mg (88%) of **56** with ee = 33%.

R_f = 0.27 (hexanes/EtOAc, 3:2); IR (neat): 2983, 2938, 1800, 1750, 1711, 1434, 1371, 1342, 1300, 1171, 1125, 1097, 1077, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74, 4.65 (AB system, 2H, $\Delta\nu_{AB}$ = 20.1 Hz, J_{AB} = 16.9 Hz, OC*H*$_2$), 2.57 (t, 2H, *J* = 7.2 Hz, COC*H*$_2$CH$_2$), 2.14 (s, 3H, COC*H*$_3$), 2.10-1.91 (m, 2H, COCH$_2$C*H*$_2$), 1.32 (s, 3H, CC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$):δ 209.2 (C*C*OC), 207.4 (C*C*OC), 176.8 (*C*OO), 72.3 (O*C*H$_2$CO), 46.5 (CH$_3$-*C*-CH$_2$), 37.4 (CO*C*H$_2$CH$_2$), 29.9 (CO*C*H$_3$), 28.3 (COCH$_2$*C*H$_2$), 20.2 (C-*C*H$_3$).

3-(3-Oxobutyl)-3-phenylfuran-2,4(3*H*,5*H*)-dione (**58**)**:**



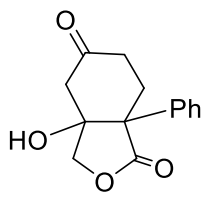
Best ee experiment: The reaction of phenyl tetronic acid (**57**) (60 mg, 0.34 mmol), methyl vinyl ketone (55 µL, 0.68 mmol), catalyst **42** (19 mg, 3.4 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 89 h according to the general procedure

provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 36 mg (43%) of **58** as a colorless liquid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 18.9 min; t_{major} = 23.5 min; 39% ee.

Best yield experiment: The reaction of phenyl tetronic acid (**57**) (60 mg, 0.34 mmol), methyl vinyl ketone (55 µL, 0.68 mmol), catalyst **37** (17 mg, 3.4 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 151 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 80 mg (95%) of **58** with ee = 14%.

R_f = 0.42 (hexanes/EtOAc, 7:3); IR (neat): 2939, 1801, 1750, 1710, 1494, 1434, 1368, 1340, 1289, 1241, 1167, 1067, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H, Ar*H*), 4.71, 4.62 (AB system, 2H, $\Delta\nu_{AB}$ = 23.3 Hz, J_{AB}= 16.5 Hz, OCH_2), 2.73-2.58 (m, 1H, COCH_2CH$_2$ or COCH$_2$CH_2), 2.56-2.28 (m, 3H, COCH_2CH_2), 2.10 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.5 (C*C*OC), 205.5 (C*C*OC), 174.3 (*C*OO), 133.5 (ArC_{ipso}), 129.5 (2 × Ar*C*), 128.8 (Ar*C*), 126.6 (2 × Ar*C*), 72.3 (O*C*H$_2$CO), 55.5 (Ph-*C*-CH$_2$), 37.9 (CO*C*H$_2$CH$_2$), 30.0 (CO*C*H$_3$), 29.2 (COCH$_2$*C*H$_2$); HRMS (APPI, pos.): *m/z* 246.0878 (246.0892 calc. for $C_{14}H_{14}O_4$, $(M)^+$) and 247.0951 (247.0970 calc. for $C_{14}H_{15}O_4$, $(M+H)^+$).

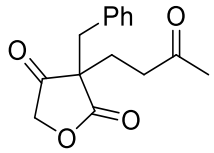
3a-Hydroxy-7a-phenyltetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione (**59**)**:**



The reaction of phenyl tetronic acid (**57**) (60 mg, 0.34 mmol), methyl vinyl ketone (55 µL, 0.68 mmol), catalyst **34** (11 µL, 6.8 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 20 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 23 mg (27%) of racemic **58** and 58 mg (67%) of **59** as a colorless liquid. HPLC of **59**: Chiralpak AS-H (hexanes/*i*-PrOH, 70:30, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 20.77 min; t_{major} = 25.92 min; 5% ee.

R_f = 0.37 (hexanes/EtOAc, 3:2); IR (neat): 3392 (br), 3324 (br), 2962, 2935, 2911, 2853, 1774, 1702, 1499, 1403, 1331, 1265, 1205, 1172, 1099, 1026, 1005, 967 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.32 (m, 5H, Ar*H*), 4.06 (dd, 1H, *J* = 9.3, 1.7 Hz, OCH_2), 3.92 (d, 1H, *J* = 9.3 Hz, OCH_2), 2.79 (s, 2H, COCH_2), 2.71-2.43 (m, 4H, COCH_2CH_2); 2.28 (br s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3 (C*C*OC), 177.4 (*C*OO), 135.0 (ArC_{ipso}), 129.5 (2 × Ar*C*), 128.9 (Ar*C*), 127.6 (2 × Ar*C*), 78.7 (OH-*C*), 74.6 (OCH_2CO), 54.9 (Ph-*C*-CH_2), 48.8 (COCH_2), 37.1 (COCH_2), 29.6 (CH_2); HRMS (APPI, pos.): *m/z* 246.0905 (246.0892 calc. for $C_{14}H_{14}O_4$, $(M)^+$) and 247.0977 (247.0970 calc. for $C_{14}H_{15}O_4$, $(M+H)^+$).

3-Benzyl-3-(3-oxobutyl)furan-2,4(3*H*,5*H*)-dione (61):[1]



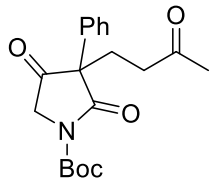
Best ee experiment: The reaction of benzyl tetronic acid (**60**) (60 mg, 0.32 mmol), methyl vinyl ketone (51 µL, 0.63 mmol), catalyst **36** (13 mg, 3.2 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 195 h according to the general procedure

provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1), 72 mg (89%) of **61** as a colorless liquid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 17.24 min; t_{major} = 20.06 min; 24% ee.

Best yield experiment: The reaction of benzyl tetronic acid (**60**) (60 mg, 0.34 mmol), methyl vinyl ketone (51 µL, 0.63 mmol), catalyst **39** (19 mg, 3.2 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 151 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1), 79 mg (96%) of **61** with ee = 11%.

R_f = 0.39 (hexanes/EtOAc, 3:2); IR (neat): 3033, 2928, 1800, 1750, 1706, 1451, 1428, 1408, 1361, 1348, 1229, 1205, 1166, 1119, 1069, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.22 (m, 3H, Ar*H*), 7.14-7.07 (m, 2H, Ar*H*), 4.37 (d, 1H, *J* = 16.8 Hz, OCH_2), 3.49 (d, 1H, *J* = 16.8 Hz, OCH_2), 3.10, 3.02 (AB system, 2H, $\Delta\nu_{AB}$ = 24.3 Hz, J_{AB} = 12.8 Hz, PhC*H*), 2.67-2.47 (m, 2H, COCH_2CH_2), 2.26-2.03 (m, 2H, COCH_2CH_2), 2.13 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$):δ 209.9 (C*C*OC), 207.2 (C*C*OC), 176.2 (*C*OO), 133.7 (ArC_{ipso}), 129.6 (2 × Ar*C*), 128.9 (2 × Ar*C*), 127.9 (Ar*C*), 73.3 (O*C*H_2CO), 54.2 (Bn-*C*-CH_2), 43.1 (Ph*C*H_2), 37.8 (CO*C*H_2CH_2), 29.9 (CO*C*H_3), 28.2 (COCH_2*C*H_2).

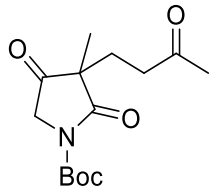
***tert*-Butyl 2,4-dioxo-3-(3-oxobutyl)-3-phenylpyrrolidine-1-carboxylate (64):**



Best ee and yield experiment: The reaction of phenyl tetramic acid (**62**) (60 mg, 0.22 mmol), methyl vinyl ketone (35 µL, 0.46 mmol), catalyst **42** (12 mg, 2.2 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 41 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 73 mg (97%) of **64** as a white solid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 90:10, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 13.01 min; t_{minor} = 15.90 min; 27% ee.

R_f = 0.41 (hexanes/EtOAc, 3:2); mp: 109-111 °C; IR (neat): 2992, 2968, 2936, 2894, 1788, 1751, 1714, 1445, 1351, 1276, 1249, 1217, 1145, 898, 852 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.29 (m, 5H, Ar*H*), 4.20 (AB system, 2H, $\Delta\nu_{AB}$ = 28.8 Hz, J_{AB}= 18.2 Hz, NCH_2), 2.66-2.46 (m, 2H, CH_2), 2.45-2.26 (m, 2H, CH_2), 2.07 (s, 3H, COCH_3), 1.56 (s, 9H, C-(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$):δ 207.4 (*C*OC), 204.0 (C*C*OC), 171.4 (N*C*OC), 149.1 (N*C*OO), 134.3 (ArC_{ipso}), 129.3 (2 × Ar*C*), 128.5 (Ar*C*), 126.7 (2 × Ar*C*), 84.4 (O-*C*(CH_3)$_3$), 60.6 (Ph-*C*-CH_2), 54.6 (N*C*H_2), 38.2 (CO*C*H_2CH_2), 30.0 (CO*C*H_3), 29.3 (COCH_2*C*H_2), 28.0 (O-C(*C*H_3)$_3$).

***tert*-Butyl 3-methyl-2,4-dioxo-3-(3-oxobutyl)pyrrolidine-1-carboxylate (65):**

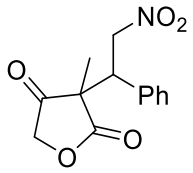


The reaction of methyl tetramic acid (**63**) (50 mg, 0.23 mmol), methyl vinyl ketone (38 µL, 0.47 mmol), catalyst **42** (13 mg, 2.3 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 27 h according to the general procedure provided, after purification

by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 51 mg (77%) of **65** as a colorless liquid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 95:5, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 18.14 min; t_{major} = 20.80 min; 26% ee.

R_f = 0.47 (hexanes/EtOAc, 1:1); IR (neat): 2980, 2935, 1794, 1757, 1734, 1712, 1453, 1440, 1369, 1343, 1307, 1277, 1252, 1149, 1091, 984, 952, 851 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (AB system, 2H, $\Delta\nu_{AB}$ = 22.7 Hz, J_{AB} = 18.6 Hz, NCH_2), 2.53 (td, 2H, *J* = 7.3, 2.1 Hz, COCH_2CH$_2$), 2.12 (s, 3H, COCH_3), 2.00 (t, 2H, *J*= 7.3 Hz, COCH$_2$CH_2), 1.57 (s, 9H, C-(CH_3)$_3$), 1.28 (s, 3H, C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.27 (C*C*OC), 207.25 (C*C*OC), 173.8 (N*C*OC), 149.2 (N*C*OO), 84.3 (O-*C*(CH$_3$)$_3$), 54.4 (N*C*H$_2$), 52.0 (CH$_3$-*C*-CH$_2$), 37.6 (CO*C*H$_2$CH$_2$), 29.9 (CO*C*H$_3$), 28.5 (COCH$_2$*C*H$_2$), 28.0 (O-C(*C*H$_3$)$_3$), 19.9 (C-CH_3).

3-Methyl-3-(2-nitro-1-phenylethyl)furan-2,4(3*H*,5*H*)-dione (**66**)**:**

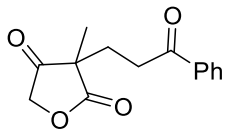


The reaction of methyl tetronic acid (**25**) (92 mg, 0.80 mmol), *β*-nitrostyrene (100 mg, 0.670 mmol), catalyst **42** (36 mg, 6.7 x 10^{-2} mmol) in DMF (2 mL) at 0 °C for 240 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5), 39 mg (22%) of **66** as a yellow solid and 55 mg (31%) as a mixture of diastereomers as a yellow solid.

Major diastereomer: R_f = 0.43 (hexanes/EtOAc, 3:1); mp: 85-93 °C; IR (neat): 2956, 2924, 1746, 1558, 1426, 1338, 1245, 1225, 1162, 1124, 1078, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 3H, Ar*H*), 7.22-7.14 (m, 2H, Ar*H*), 5.09 (ABX, 2H, $\Delta\nu_{AB}$ = 34.6 Hz, J_{AB} = 13.6 Hz, J_{AX} = 10.2 Hz, J_{BX} = 5.0 Hz, CH_2NO_2), , 4.38 (d, 1H, *J* = 17.2 Hz, OCH_2), 3.94 (dd, 1H, *J* = 10.2, 5.0 Hz, PhC*H*), 3.49 (d, 1H, *J* = 17.2 Hz, OCH_2), 1.47 (s, 3H, C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$):δ 207.7 (C*C*OC), 175.6 (*C*OO), 133.7 (ArC_{ipso}), 129.5 (2 × Ar*C*), 129.2 (Ar*C*), 128.3 (2 × Ar*C*), 74.5 (O*C*H_2 or *C*H_2NO_2), 72.6 (O*C*H_2 or *C*H_2NO_2), 51.02 (OC-*C*-COO), 48.0 (Ph*C*H), 18.5 (C*C*H_3); MS (APPI, neg.): *m/z* 263.0800 (263.0794 calc. for $C_{13}H_{13}NO_5$, $(M)^-$) and 290.0670 (290.0665 calc. for $C_{14}H_{12}NO_6$, $((M+HCOO)–H_2O)^–$.

Minor diastereomer (mixture with major diastereomer): R_f = 0.42 (hexanes/EtOAc, 3:1); IR (neat): 2952, 2922, 1797, 1747, 1555, 1426, 1378, 1244, 1081, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.29 (m, 3H, Ar*H*), 7.25-7.16 (m, 2H, Ar*H*), 5.03 (d, 2H, *J* = 7.8 Hz, CH_2NO_2), 4.48 (d, 1H, *J* = 17.3 Hz, OCH_2), 4.04 (t, 1H, *J* = 7.8 Hz, PhC*H*), 4.0 (d, 1H, *J* = 17.3 Hz, OCH_2), 1.41 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$):δ 209.6 (C*C*OC), 174.9 (*C*OO), 133.7(ArC_{ipso}), 129.4 (2 × Ar*C*), 129.3 (Ar*C*), 128.4 (2 × Ar*C*), 74.0 (O*C*H_2 or *C*H_2NO_2), 72.5 (O*C*H_2 or *C*H_2NO_2), 51.0 (OC-*C*-COO), 47.5 (Ph*C*H), 19.2 (C-*C*H_3).

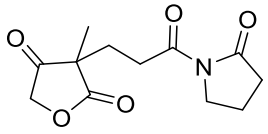
3-Methyl-3-(3-oxo-3-phenylpropyl)furan-2,4(3*H*,5*H*)-dione (81):



The reaction of methyl tetronic acid (**25**) (60 mg, 0.53 mmol), phenyl vinyl ketone (139 mg, 1.05 mmol), catalyst **42** (28 mg, 5.3 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 20 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5), 126 mg (98%) of **81** as yellow solid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 20.16 min; t_{minor} = 26.95 min; 13% ee.

R_f = 0.28 (hexanes/EtOAc, 4:1); mp: 89-93 °C; IR (neat): 2948, 2922, 1788, 1748, 1673, 1594, 1578, 1446, 1427, 1379, 1366, 1345, 1298, 1281, 1216, 1199, 1145, 1079, 1, 857 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93-7.86 (m, 2H, Ar*H*), 7.60-7.53 (m, 1H, Ar*H*), 7.49-7.41 (m, 2H, Ar*H*), 4.73 (AB system, 2H, $\Delta\nu_{AB}$ = 38.4 Hz, J_{AB} = 16.8 Hz, OCH_2), 3.21-3.00 (m, 2H, CH_2CH_2CO), 2.30-2.11 (m, 2H, CH_2CH_2CO), 1.38 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$):δ 209.1 (*C*O), 198.9 (*C*O), 176.9 (*C*OO), 136.2 (ArC_{ipso}), 133.5 (Ar*C*), 128.7 (2 × Ar*C*), 128.0 (2 × Ar*C*), 72.3 (OCH_2CO), 46.7 (OC-*C*-COO), 32.6 ($COCH_2CH_2$), 28.8 ($COCH_2CH_2$), 20.5 (C-CH_3); HRMS (APPI, pos.): *m/z* 246.0881 (246.0892 calc. for $C_{14}H_{14}O_4$, $(M)^+$) and 247.0953 (247.0970 calc. for $C_{14}H_{15}O_4$, $(M+H)^+$).

3-Methyl-3-(3-oxo-3-(2-oxopyrrolidin-1-yl)propyl)furan-2,4(3*H*,5*H*)-dione (82):

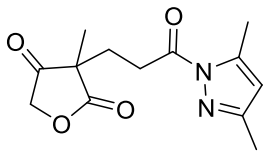


The reaction of methyl tetronic acid (**25**) (60 mg, 0.53 mmol), Michael acceptor **69** (146 mg, 1.05 mmol), catalyst **42** (29 mg, 5.3 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 41 h according to the general procedure provided, after purification

by flash column chromatography on silica gel (hexanes/EtOAc, 3:2), 131 mg (98%) of **82** as a pale-yellow liquid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 33.67 min; t_{minor} = 38.85 min; 7% ee.

R_f = 0.26 (hexanes/EtOAc, 3:2); IR (neat): 2982, 2939, 2901, 1802, 1735, 1682, 1455, 1434, 1388, 1361, 1254, 1224, 1193, 1073, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.69 (AB system, 2H, $\Delta\nu_{AB}$ = 32.5 Hz, J_{AB}= 16.7 Hz, OCH_2), 3.78-3.70 (br ddd, 2H, *J* = 8.3, 6.1, 1.0 Hz, NCH_2), 3.09-2.89 (m, 2H, NCOCH_2), 2.59 (A_2X_2 system, 2H, J_{AX} = 7.6 Hz, COCH_2CH_2), 2.14 (A_2B_2 system, 2H, *J* = 7.6 Hz, COCH_2CH_2), 2.09-1.97 (m, 2H, NCOCH_2CH_2), 1.35 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$):δ 209.4 (C*C*OC), 176.9 (*C*OO or *C*ON), 175.5 (*C*OO or *C*ON), 173.0 (*C*OO or *C*ON), 72.4 (O*C*H_2CO), 47.0 (OC-*C*-CO), 45.4 (N-*C*H_2), 33.5 (*C*H_2), 31.4 (*C*H_2), 29.1 (*C*H_2), 21.0 (C-*C*H_3), 17.2 (*C*H_2). HRMS (APPI, pos.): *m/z* 253.0942 (253.0950 calc. for $C_{12}H_{15}NO_5$, $(M)^+$) and 254.1017 (254.1028 calc. for $C_{12}H_{16}NO_5$, $(M+H)^+$).

3-(3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-oxopropyl)-3-methylfuran-2,4(3*H*,5*H*)-dione (83):

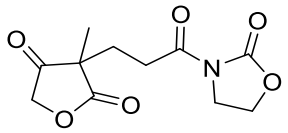


The reaction of methyl tetronic acid (**25**) (60 mg, 0.53 mmol), Michael acceptor **70** (158 mg, 1.05 mmol), catalyst **42** (29 mg, 5.3 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 21 h according to the general procedure provided, after purification

by flash column chromatography on silica gel (hexanes/EtOAc, 4:1), 130 mg (93%) of **83** as a colorless liquid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 98:2, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 31.45 min; t_{minor} = 34.99 min; 21% ee.

R_f = 0.49 (hexanes/EtOAc, 3:2); IR (neat): 3273 (br), 3148, 2971, 2931, 2876, 1712, 1577, 1457, 1457, 1415, 1379, 1270, 1213, 1166, 1075, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.95 (br d, 1H, *J* = 1.0 Hz, C=C-*H*), 4.71 (AB system, 2H, $\Delta\nu_{AB}$ = 27.1 Hz, J_{AB} = 16.8 Hz, OC*H*$_2$CO), 3.31-3.08 (m, 2H, COC*H*$_2$CH$_2$), 2.48 (br d, 3H, *J* = 1.0 Hz, C=CC*H*$_3$), 2.31-2.13 (m, 2H, COCH$_2$C*H*$_2$), 2.21 (s, 3H, C=CC*H*$_3$), 1.39 (s, 3H, CC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2 (C*C*OC), 176.7 (*C*OO or *C*ON), 172.6 (*C*OO or *C*ON), 152.4 (N=*C*), 144.1 (N─*C*(CH$_3$)=C), 111.4 (C=*C*H), 72.4 (O*C*H$_2$COO), 47.0 (OC-*C*-COO), 29.9 (*C*H$_2$), 29.2 (*C*H$_2$), 20.9 (*C*H$_3$), 14.4 (*C*H$_3$), 13.8 (*C*H$_3$).

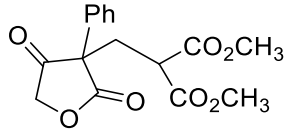
3-Methyl-3-(3-oxo-3-(2-oxooxazolidin-3-yl)propyl)furan-2,4(3*H*,5*H*)-dione (84):



The reaction of methyl tetronic acid (**25**) (60 mg, 0.53 mmol), Michael acceptor **71** (148 mg, 1.05 mmol), catalyst **42** (29 mg, 5.3 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 3 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3), 109 mg (81%) of **84** as a white solid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 16.41 min; t_{major} = 25.80 min; 2% ee.

R_f = 0.27 (hexanes/EtOAc, 1:1); mp: 96-102 °C; IR (neat): 2995, 2939, 1750, 1680, 1451, 1434, 1395, 1367, 1344, 1299, 1223, 1163, 1138, 1120, 1094, 1080, 1036, 1010, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.69 (AB system, 2H, $\Delta\nu_{AB}$ = 26.1 Hz, J_{AB} = 16.8 Hz, OC*H*$_2$CO), 4.42 (t, 2H, *J* = 7.5 Hz, NCH$_2$C*H*$_2$), 4.03-3.88 (m, 2H, NC*H*$_2$CH$_2$), 3.12-2.93 (m, 2H, COC*H*$_2$CH$_2$), 2.16 (t, 2H, *J* = 7.5 Hz, COCH$_2$C*H*$_2$), 1.36 (s, 3H, CC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2 (C*C*OC), 176.7 (*C*O), 172.3 (*C*O), 153.4 (O*C*ON), 72.4 (O*C*H$_2$CO), 62.2 (NCH$_2$*C*H$_2$O), 46.9 (OC-*C*-CO), 42.4 (N-*C*H$_2$), 29.8 (*C*H$_2$), 28.8 (*C*H$_2$), 21.1 (C-*C*H$_3$); HRMS (APPI, pos.): *m/z* 255.0726 (255.0743 calc. for $C_{11}H_{13}NO_6$, $(M)^+$), 256.0799 (256.0821 calc. for $C_{11}H_{14}NO_6$, $(M+H)^+$) and 273.1064 (273.1087 calc. for $C_{11}H_{17}N_2O_6$, $(M+NH_4)^+$).

Dimethyl 2-((2,4-dioxo-3-phenyltetrahydrofuran-3-yl)methyl)malonate (85):

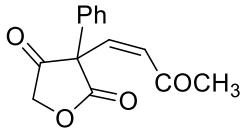


The reaction of phenyl tetronic acid (**57**) (60 mg, 0.34 mmol), dimethyl 2-methylenemalonate (**72**) (98 mg, 0.68 mmol), catalyst **42** (19 mg, 3.4 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 120 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5), 16 mg (15%) of **85** as a colorless. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_1 = 11.98 min; t_2 = 25.33 min; racemic.

R_f = 0.37 (hexanes/EtOAc, 3:1); IR (neat): 3006, 2956, 1801, 1751, 1727, 1494, 1436, 1339, 1259, 1237, 1199, 1154, 1124, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.30

(m, 5H, Ar*H*), 4.63 (AB system, 2H, $\Delta\nu_{AB}$ = 31.3 Hz, J_{AB} = 16.2 Hz, OCH_2), 3.76-3.71 (m, 1H, CH_2C*H*), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.75 (ABX, 2H, J_{AB} = 14.8 Hz, J_{AX} = 8.3 Hz, J_{BX} = 7.0 Hz, CH_2CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7 (C*C*OC), 173.9 (*C*OO), 169.4 (*C*OO), 169.1 (*C*OO), 133.6 (ArC_{ipso}), 129.8 (2 × Ar*C*), 129.2 (Ar*C*), 126.8 (2 × Ar*C*), 72.5 (O*C*H_2CO), 55.6 (Ph-*C*-CH_2), 53.0 (O*C*H_3), 52.9 (O*C*H_3), 47.2 (CH_2*C*H), 33.7 (*C*H_2CH); HRMS (APPI, pos.): *m/z* 320.0911 (320.0896 calc. for $C_{16}H_{16}O_7$, $(M)^+$) and 321.0986 (321.0974 calc. for $C_{16}H_{17}O_7$, $(M+H)^+$).

(*Z*)-3-(3-Oxobut-1-en-1-yl)-3-phenylfuran-2,4(3*H*,5*H*)-dione (86):

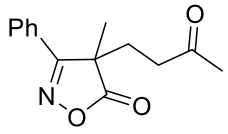


The reaction of phenyl tetronic acid (**57**) (50 mg, 0.28 mmol), but-3-yn-2-one (**80**) (44 µL, 0.57 mmol), catalyst **42** (15 mg, 2.8 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 66 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:2), 19 mg (28%) of **86** as a colorless white solid. HPLC: Chiralpak AS-H (hexanes/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, λ = 254 nm): t_1 = 8.7; t_2 = 14.5 min; racemic.

R_f = 0.57 (hexanes/EtOAc, 7:3); mp: 116-121 °C; IR (neat): 3060, 2923, 2853, 1801, 1749, 1685, 1603, 1492, 1435, 1405, 1340, 1271, 1210, 1193, 1084, 1072, 1052, 1001, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.37 (m, 5H, Ar*H*), 6.46, 6.29 (AX, 2H, $\Delta\nu_{AB}$ = 109.3 Hz, J_{AB} = 10.7 Hz, *H*C=C*H*), 4.97, 4.65 (AX, 2H, $\Delta\nu_{AB}$ = 94.0 Hz, J_{AB} = 15.6 Hz, OCH_2), 2.30 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9 (C*C*OC), 198.5 (C*C*OC), 171.5

(*C*OO), 142.8 (OC=*C*H), 135.1 (Ar*C*$_{ipso}$), 129.8 (2 × Ar*C*), 129.2 (C=*C*H or Ar*C*), 128.9 (C=*C*H or Ar*C*), 127.1 (2 × Ar*C*), 74.2 (O*C*H$_2$), 60.9 (Ph-*C*-CH), 31.0 (CO*C*H$_3$); HRMS (APPI, pos.): *m/z* 244.0729 (244.0736 calc. for $C_{14}H_{12}O_4$, $(M)^+$) and 245.0803 (245.0814 calc. for $C_{14}H_{13}O_4$, $(M+H)^+$).

4-Methyl-4-(3-oxobutyl)-3-phenylisoxazol-5(4*H*)-one (88):

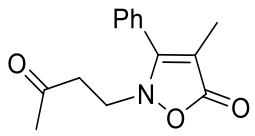


The reaction of isoxazol-5(4*H*)-one **87** (60 mg, 0.34 mmol), methyl vinyl ketone (56 µL, 0.69 mmol), catalyst **42** (19 mg, 3.4 x 10^{-2} mmol) in dichloromethane (2 mL) at room temperature for 17 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:1), 36 mg (43%) of **88** as colorless liquid and 46 mg (55%) of **89** brown solid. HPLC of **88**: Chiralcel OD-H (hexanes/*i*-PrOH, 93:7, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 8.10 min; t_{major} = 9.22 min; 8% ee.

R_f = 0.57 (hexanes/EtOAc, 7:3); IR (neat): 3063, 2978, 2936, 1788, 1714, 1553, 1454, 1418, 1358, 1226, 1164, 1144, 1093, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.73 (m, 2H, Ar*H*), 7.59-7.44 (m, 3H, Ar*H*), 2.49-2.17 (m, 4H, COC*H*$_2$C*H*$_2$), 2.08 (s, 3H, COC*H*$_3$), 1.64 (s, 3H, CC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7 (C*C*OC), 180.9 (*C*O), 168.2 (N=*C*), 132.0 (Ar*C*), 129.4 (2 × Ar*C*), 127.4 (Ar*C*$_{ipso}$), 126.7 (2 × Ar*C*), 49.5 (OC-*C*-CO), 38.2 (CO*C*H$_2$CH$_2$), 30.4 (COCH$_2$*C*H$_2$), 30.0 (*C*H$_3$), 22.2 (*C*H$_3$); HRMS (APPI, pos.): *m/z* 245.1042 (245.1052 calc. for $C_{14}H_{15}NO_3$, $(M)^+$) and 426.1115 (246.1130 calc.

for $C_{14}H_{16}NO_3$, $(M+H)^+$).

4-Methyl-2-(3-oxobutyl)-3-phenylisoxazol-5(2*H*)-one (89):



R_f = 0.22 (hexanes/EtOAc, 7:3); mp: 63-69 ºC; IR (neat): 2962, 2925, 2871, 2851, 1726, 1704, 1635, 1447, 1366, 1330, 1254, 1186, 1166, 1066, 1011, 866 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57-7.45 (m, 5H, Ar*H*), 3.53 (t, 2H, *J* = 6.6 Hz, NC*H*$_2$CH$_2$), 2.84 (t, 2H, *J* = 6.6 Hz, NCH$_2$C*H*$_2$), 2.18 (s, 3H, COC*H*$_3$), 1.93 (s, 3H, CC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7 (C*C*OC), 172.1 (*C*OO), 164.7 (Ph*C*=C), 131.0 (Ar*C*), 129.2 (2 × Ar*C*), 128.4 (2 × Ar*C*), 127.8 (ArC_{ipso}), 102.2 (PhC=*C*), 49.0 (N*C*H$_2$CH$_2$), 39.4 (NCH$_2$*C*H$_2$), 30.5 (CO*C*H$_3$), 7.7 (*C*H$_3$C=C); HRMS (APPI, pos.): *m/z* 245.1022 (245.1052 calc. for $C_{14}H_{15}NO_3$, $(M)^+$) and 246.1095 (246.1130 calc. for $C_{14}H_{16}NO_3$, $(M+H)^+$).

2.7 References

1. Ramachary, D. B.; Kishor, M. *Org. Biomol. Chem.*, **2010**, *8*, 2859.

2. (a) Bacigaluppo, J. A.; Colombo, M. I.; Cravero, R. M.; González-Sierra, M.; Preite, M. D.; Zinczuk, J.; Rúveda, E. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1877. (b) Bacigaluppo, J. A.; Colombo, M. I.; M.; Preite, M. D.; Zinczuk, J.; Rúveda, E. A. *Tetrahedron: Asymmetry* **1996**, *7*, 1041.

3. (a) Winkler, J.D.; Doherty, E. M. *J. Am.Chem. Soc.*, **1999**, *121*, 7425. (b) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.*, **2005**, ***7***, 2413. (c) Tambar, U. K.; Kano, T.; Stoltz, B. M. *J. Org. Chem.*, **2006**, *71*, 8357. (d) Boeckman, R. K.; Ferreira, M. R. D. R.; Mitchell, L. H.; Shao, P.; Neeb, M. J.; Fang, Y. *Tetrahedron* **2011**, *67*, 9787.

4. Colombo, M. I.; Zinczuk, J.; Bohn, M. L.; Ruveda, E. A. *Tetrahedron: Asymmetry* **2003**, *14*, 717.

5. Okamura, H.; Yamauchi, K.; Miyawaki, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett*. **1997**, *38*, 263.

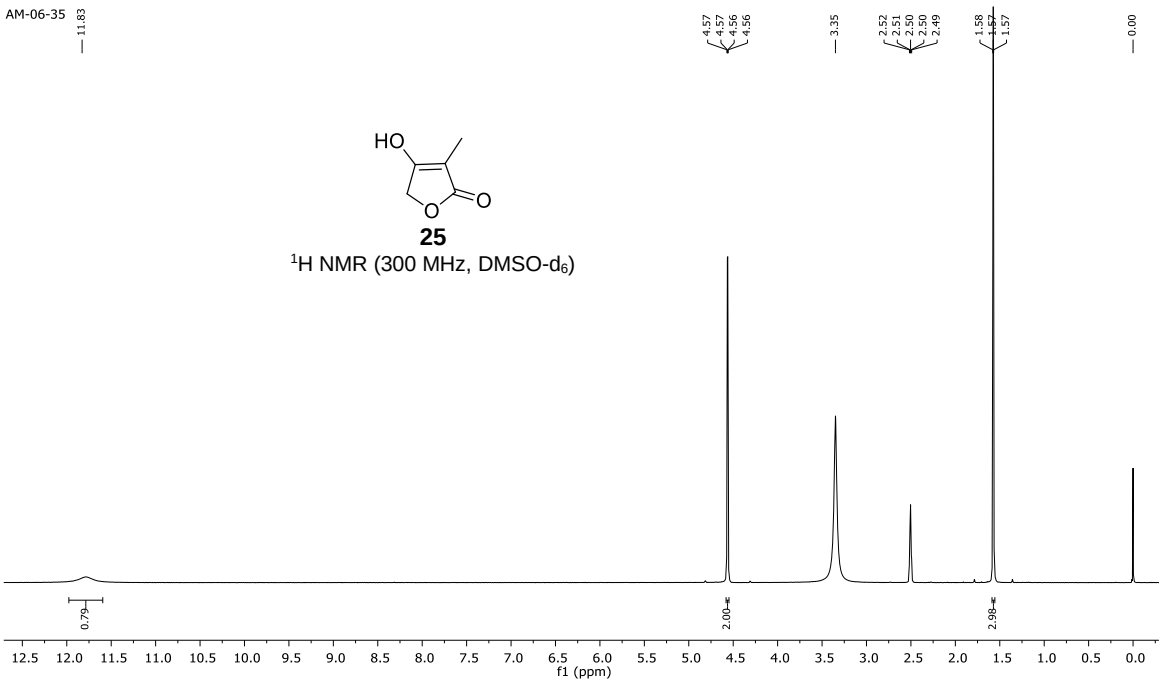
6. White, J.D.; Takabe, K.; Prisbylla, M.P. *J. Org. Chem.* **1985**, *50*. 5233.

7. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; (c) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048; (d) Liu, T. -Y.; Long, J.; Li, B. -J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y. -C. *Org. Biomol. Chem.* **2006**, *4*, 2097; (e) Li, B. -J.; Jiang, L.; Liu, M.; Chen, Y. -C.; Ding, L. -S.; Wu, Y. *Synlett*, **2005**, 603; (f) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481; (g) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153; (h)

Konishi, H.; Lam, T.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028; (i) Qian, Y.; Ma, G.; Lv, A.; Zhu, H. - L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 3004; (j) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (k) Chang, X.; Wang, Q.; Wang, Y.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2013**, 2164. (l) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, 7, 4713.

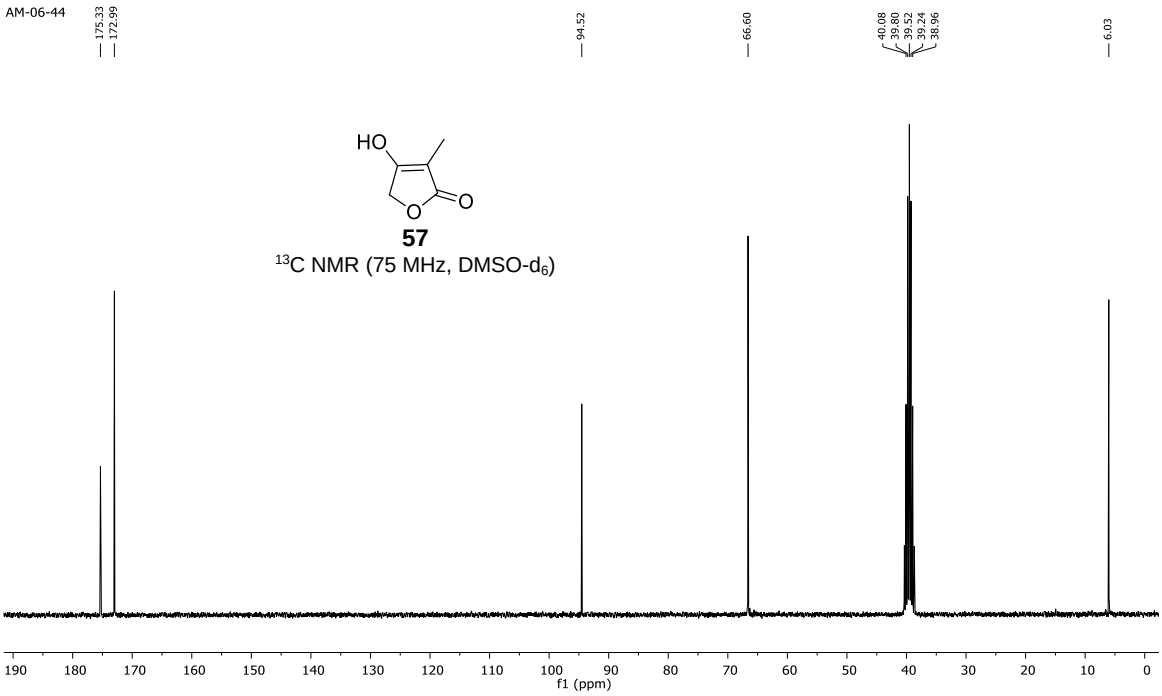
8. Prevost, S.; Phansavath, P.; Haddad, M. *Tetrahedron: Asymmetry*, **2010**, *21*, 16.
9. (a) Ravía, S. P.; Carrera, I.; Seoane, G. A.; Vero, S.; Gamenara, D. *Tetrahedron: Asymmetry* **2009**, *20*, 1393. (b) Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. *J. Org. Chem.***2006,** *71*, 8357.
10. (a) Yang, W.; Liu, J.; Zhang, H. *Tetrahedron Lett.* **2010,** *51*, 4874. (b) Yang, W.; Liu, J.; Zhang, H. Tetrahedron Lett. **2010**, *51*, 4874.
11. (a) Hu, M.; Rong, J.; Miao, W.; Ni, C.; Han, Y.; Hu, J. *Org. Lett*. **2014**, *16*, 2030. (b) Haque, Md. A.; Nishino, H. *Heterocycles*, **2011**, *83*, 1783.
12. (a) Pintori, D. G.; Greaney M. F. *Org. Lett.*, **2011**, *13*, 5713. (b) Miyazaki, H.; Ogiku, T.; Sai, H.; Moritani, Y.; Ohtani, A.; Ohmizu, H. *Chem. Pharm. Bull.* **2009**, *57*, 979.
13. Rahman, Md. T.; Haque, Md. A.; Igarashi, H.; Nishino, H. *Molecules* **2011**, *16*, 9562.

2.8 Selected ^{1}H NMR and ^{13}C NMR Spectra



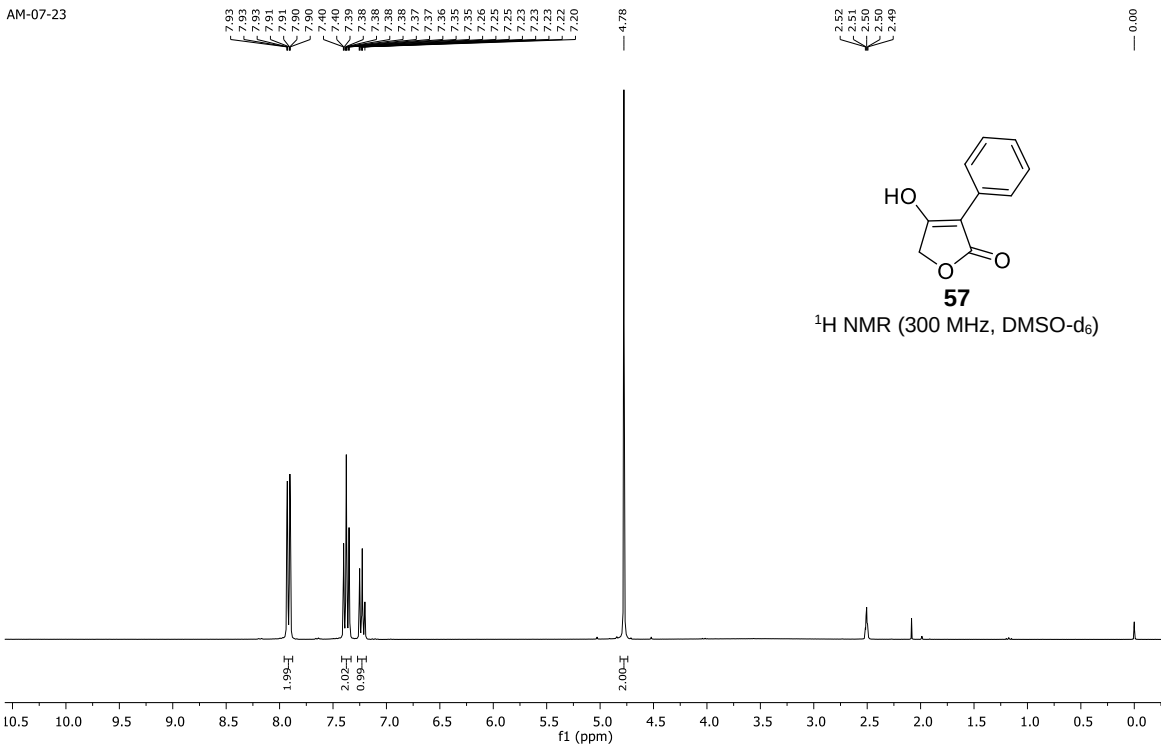
25

^{1}H NMR (300 MHz, DMSO-d_6)



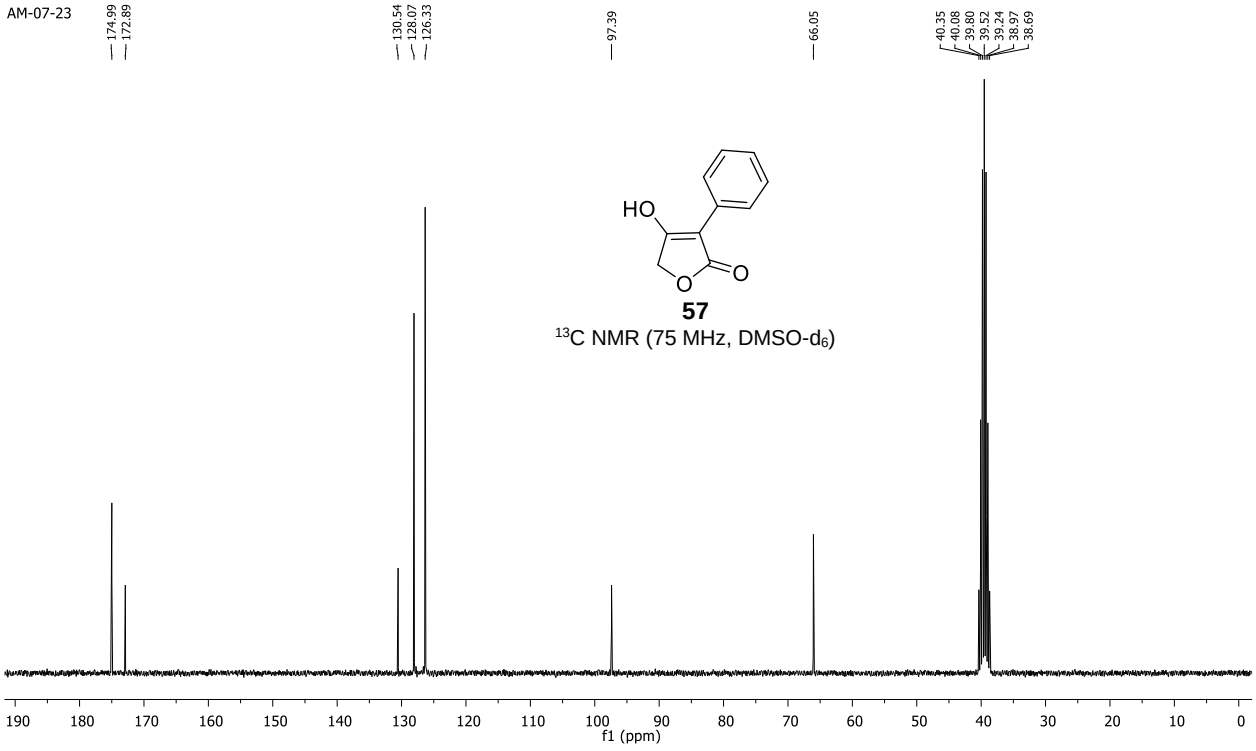
57

^{13}C NMR (75 MHz, DMSO-d_6)



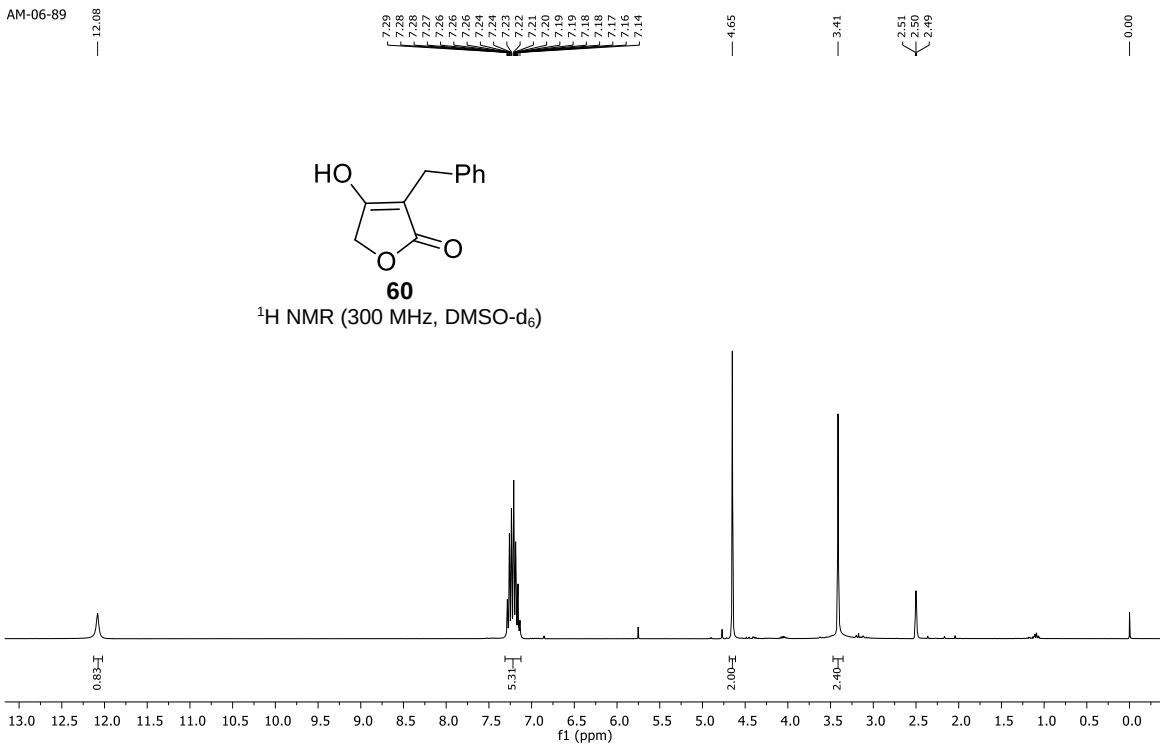
57

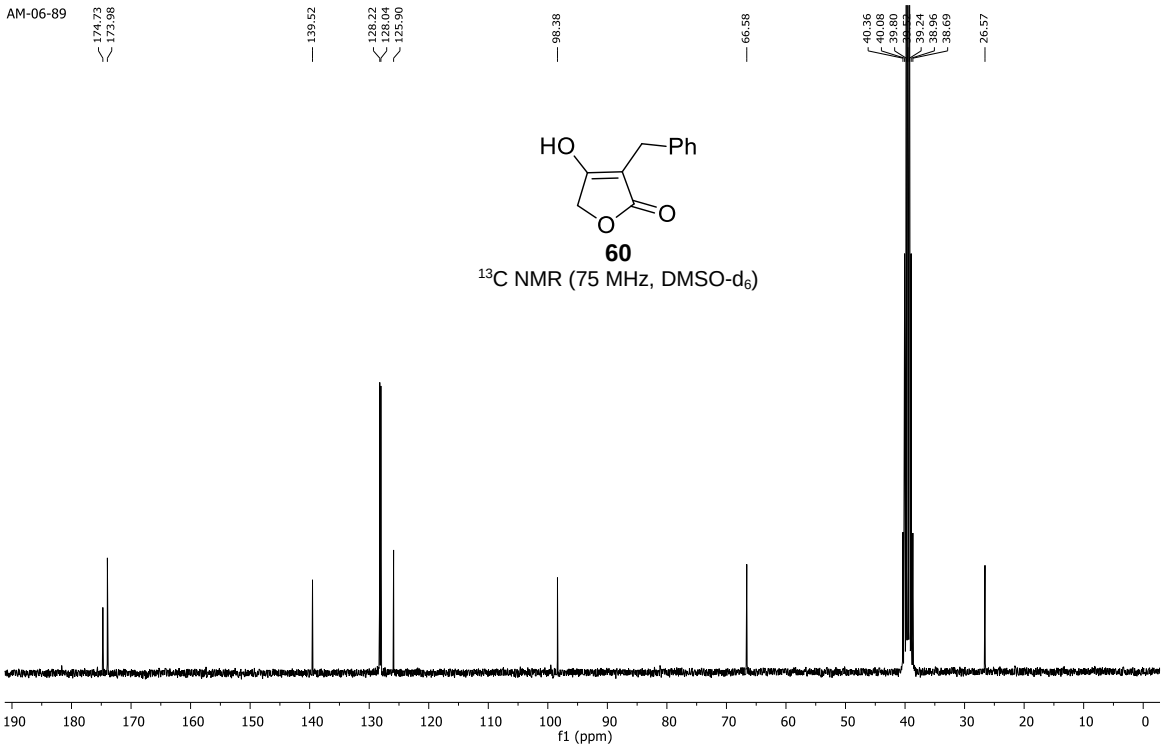
^{1}H NMR (300 MHz, DMSO-d_6)

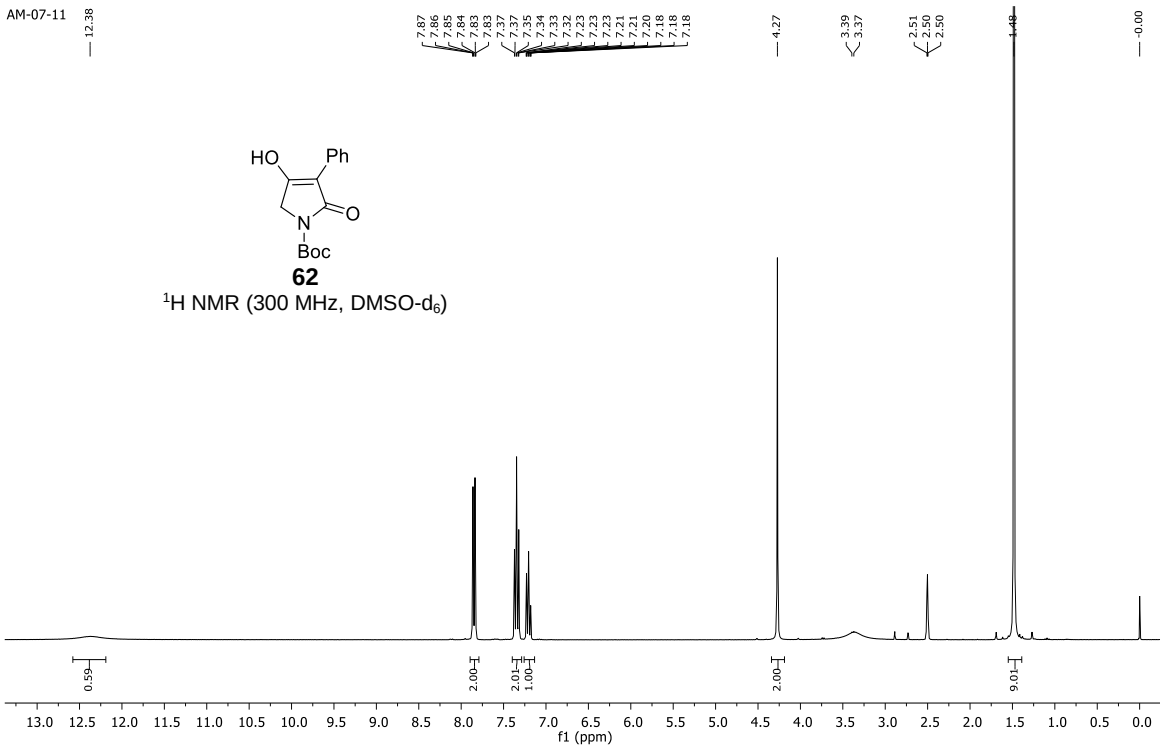


57

^{13}C NMR (75 MHz, DMSO-d_6)

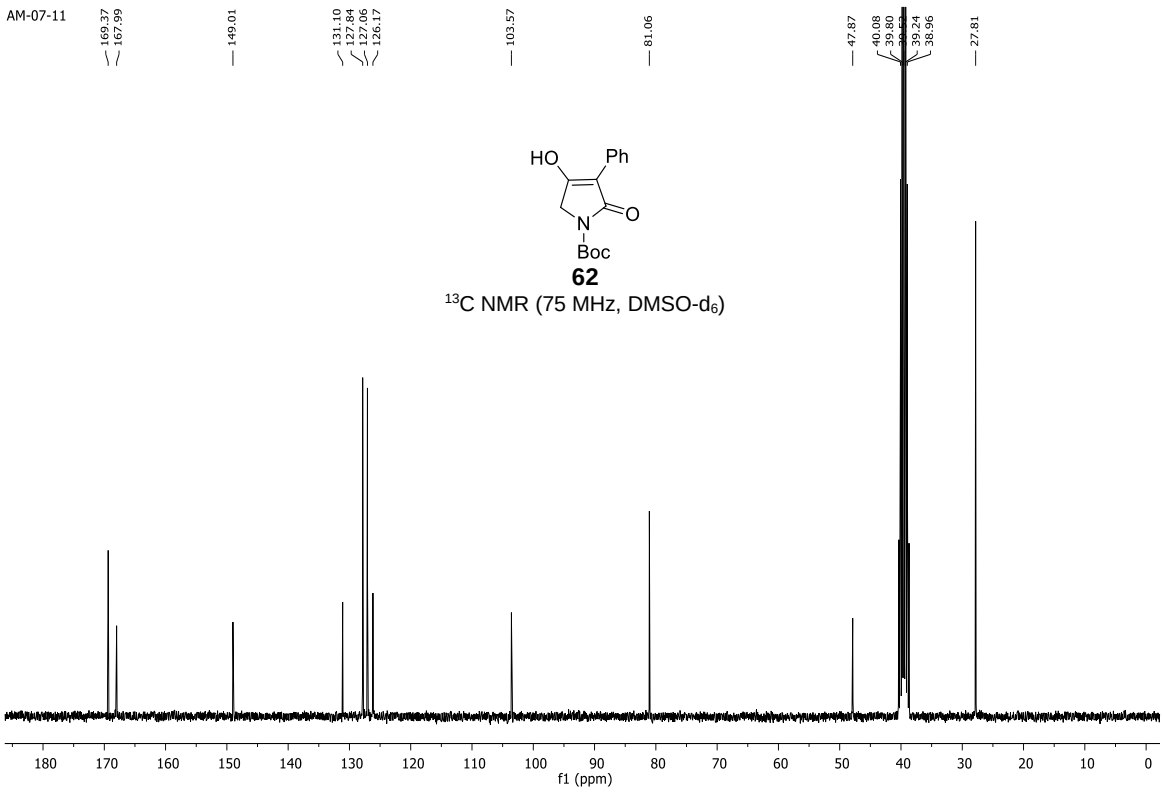

AM-06-89
12.08
7.29
7.28
7.28
7.27
7.26
7.26
7.26
7.24
7.24
7.23
7.22
7.21
7.20
7.19
7.19
7.18
7.18
7.17
7.16
7.14
4.65
3.41
2.51
2.50
2.49
0.00
HO
Ph
O
O
60
1H NMR (300 MHz, DMSO-d6)
0.83
5.31
2.00
2.40
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


AM-06-89
174.73
173.98
139.52
128.22
128.04
125.90
98.38
66.58
40.36
40.08
39.80
39.52
39.24
38.96
38.69
26.57
HO
Ph
O
O
60
13C NMR (75 MHz, DMSO-d6)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



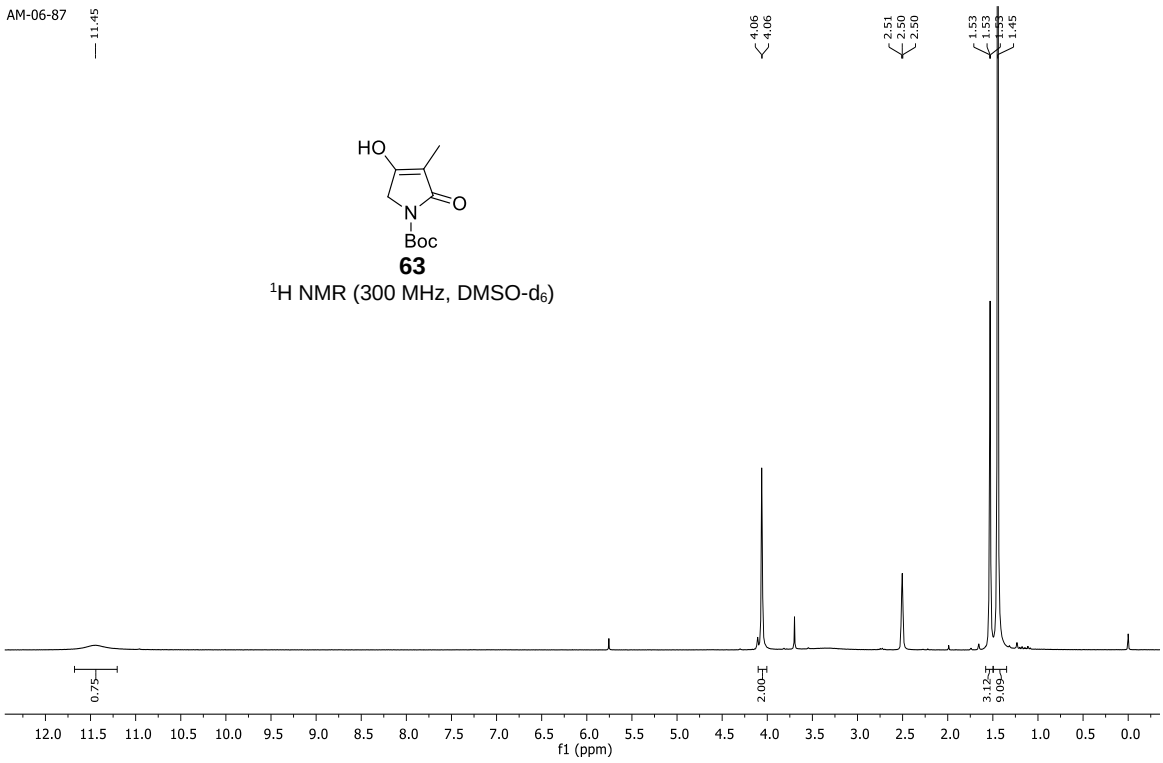
62

^{1}H NMR (300 MHz, DMSO-d_6)



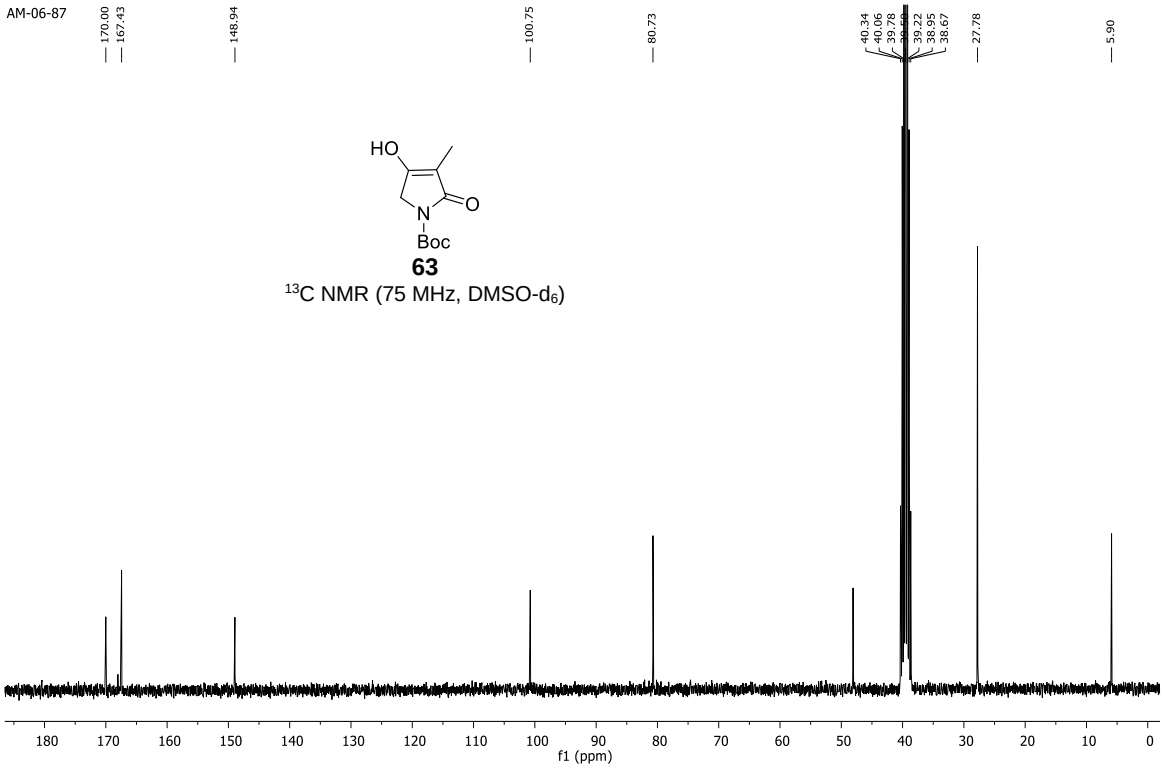
62

^{13}C NMR (75 MHz, DMSO-d_6)



63

^{1}H NMR (300 MHz, DMSO-d_6)



63

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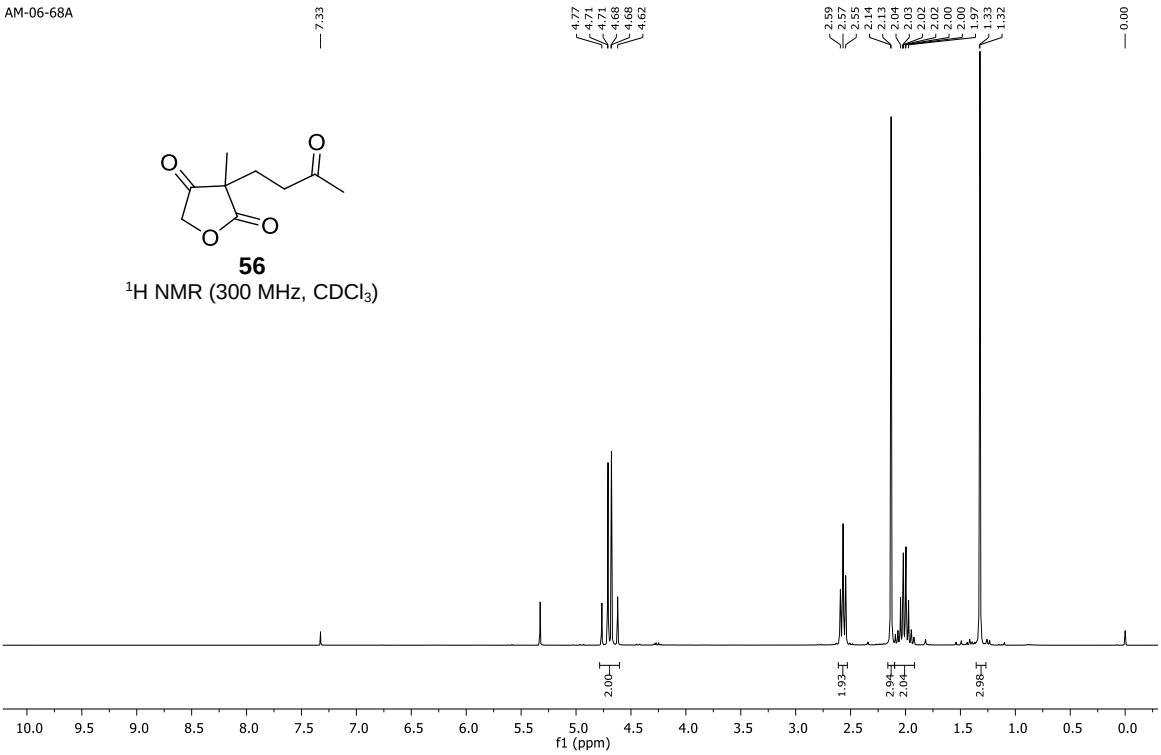
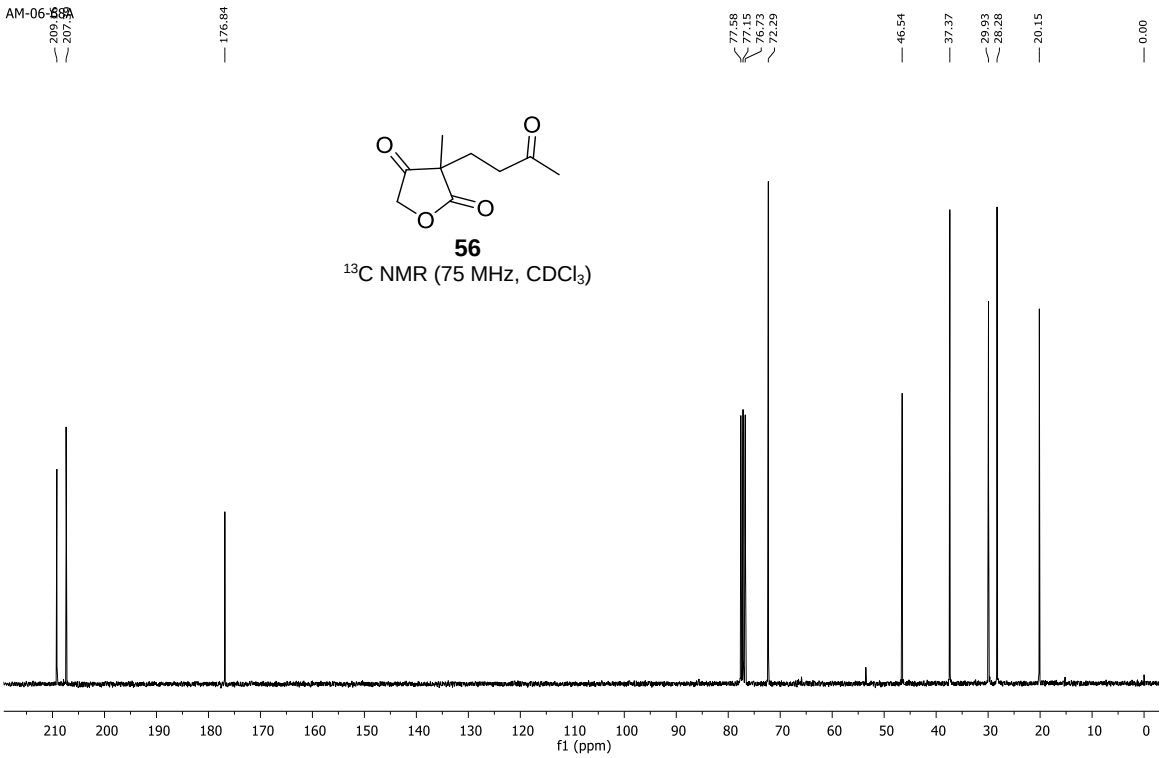


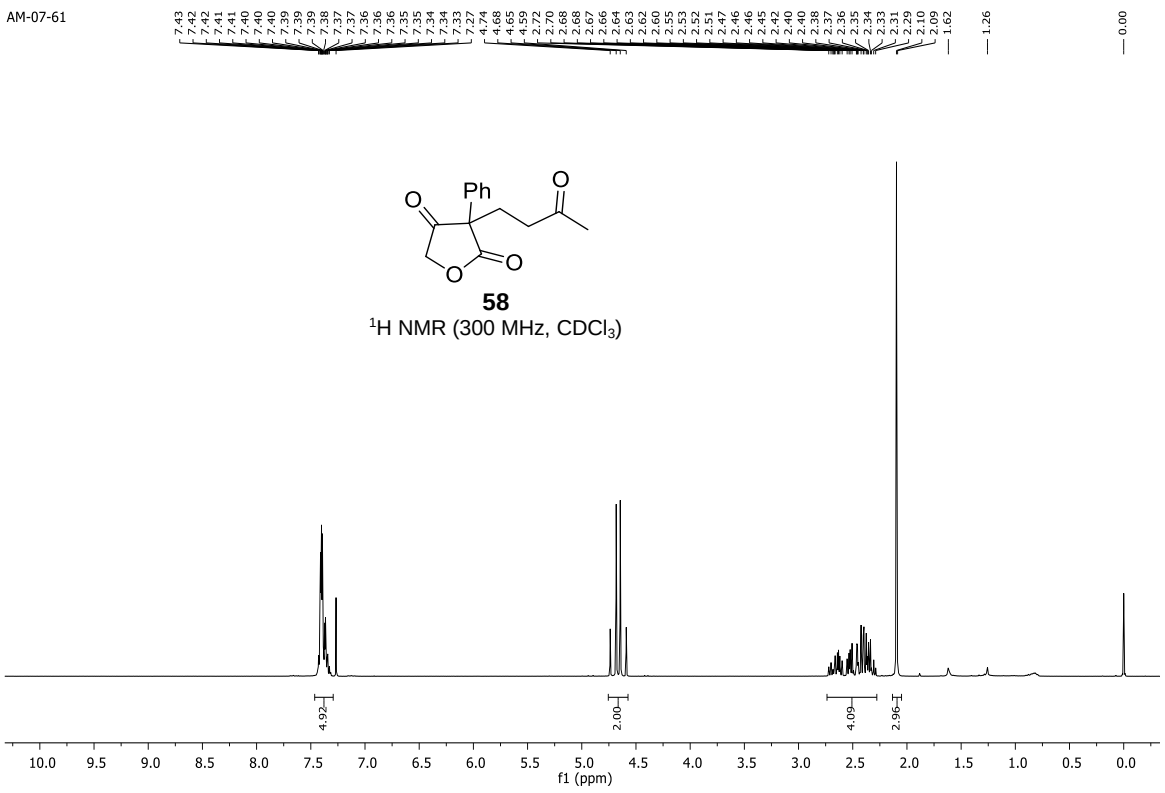
56

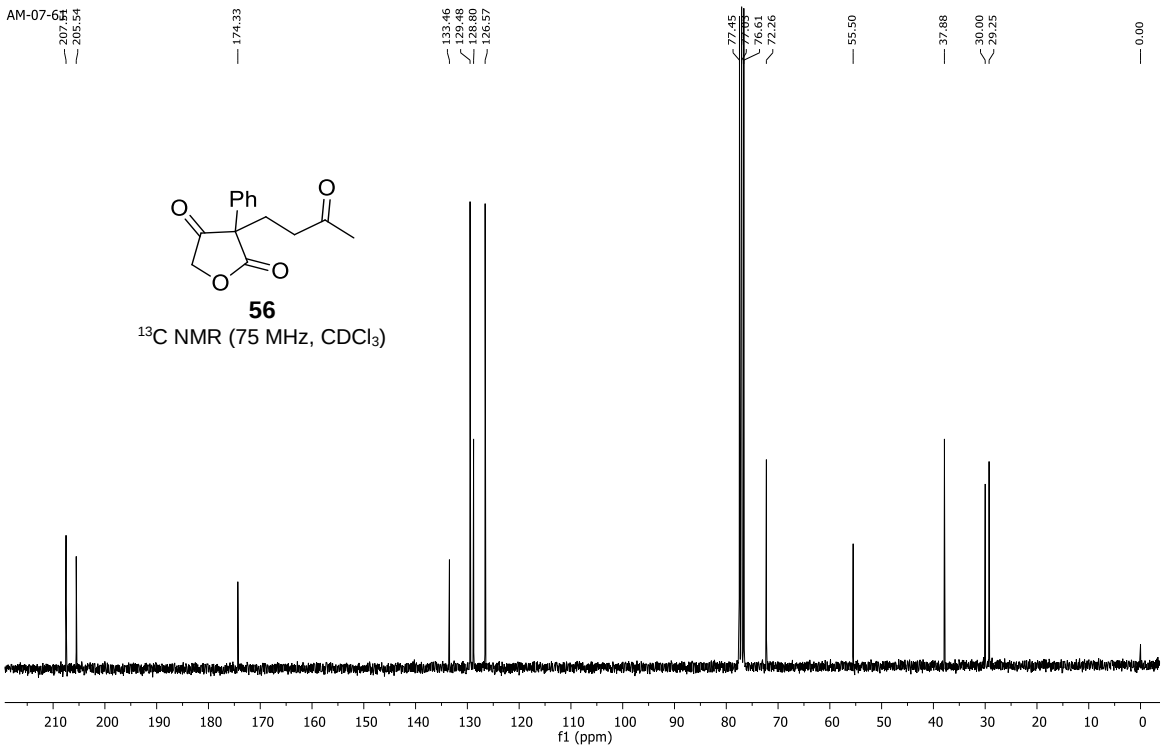
^{1}H NMR (300 MHz, $CDCl_3$)



56

^{13}C NMR (75 MHz, $CDCl_3$)


AM-07-61
Ph
O
O
O
O
58
1H NMR (300 MHz, CDCl3)
4.92
2.00
4.09
2.96
f1 (ppm)


AM-07-61
207.11
205.54
174.33
133.46
129.48
128.80
126.57
77.45
77.03
76.61
72.26
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37.88
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29.25
0.00
Ph
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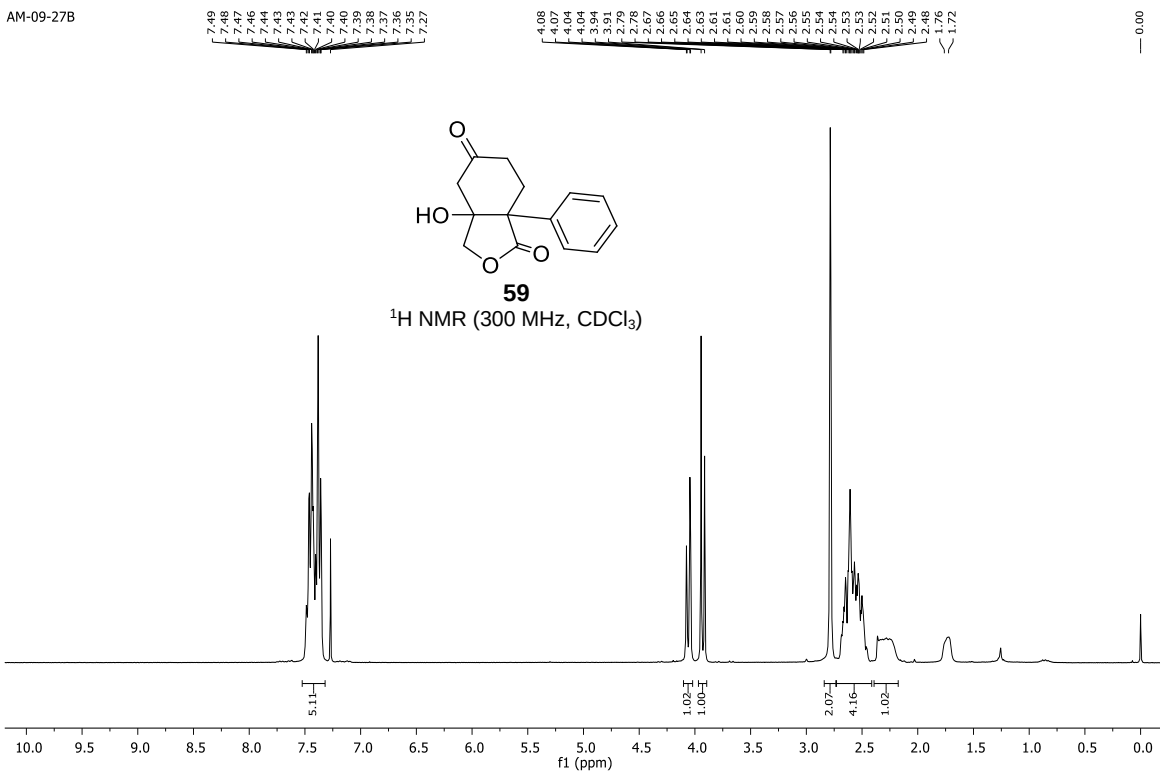
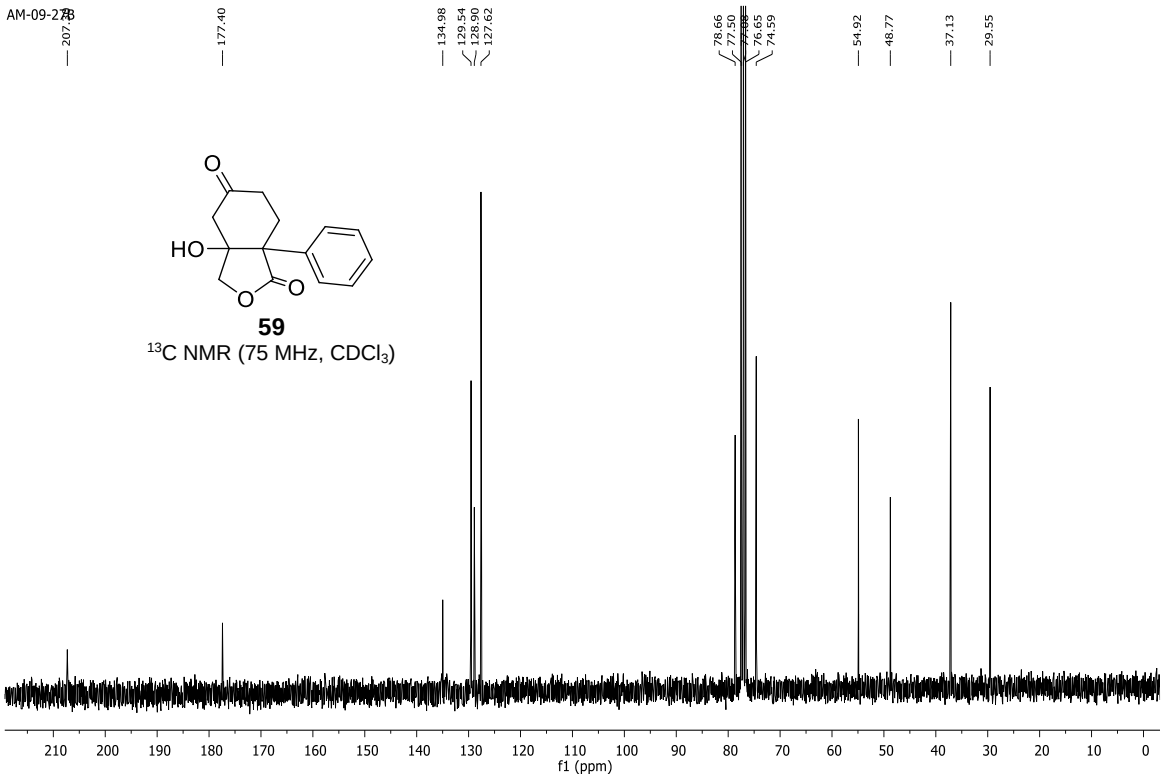
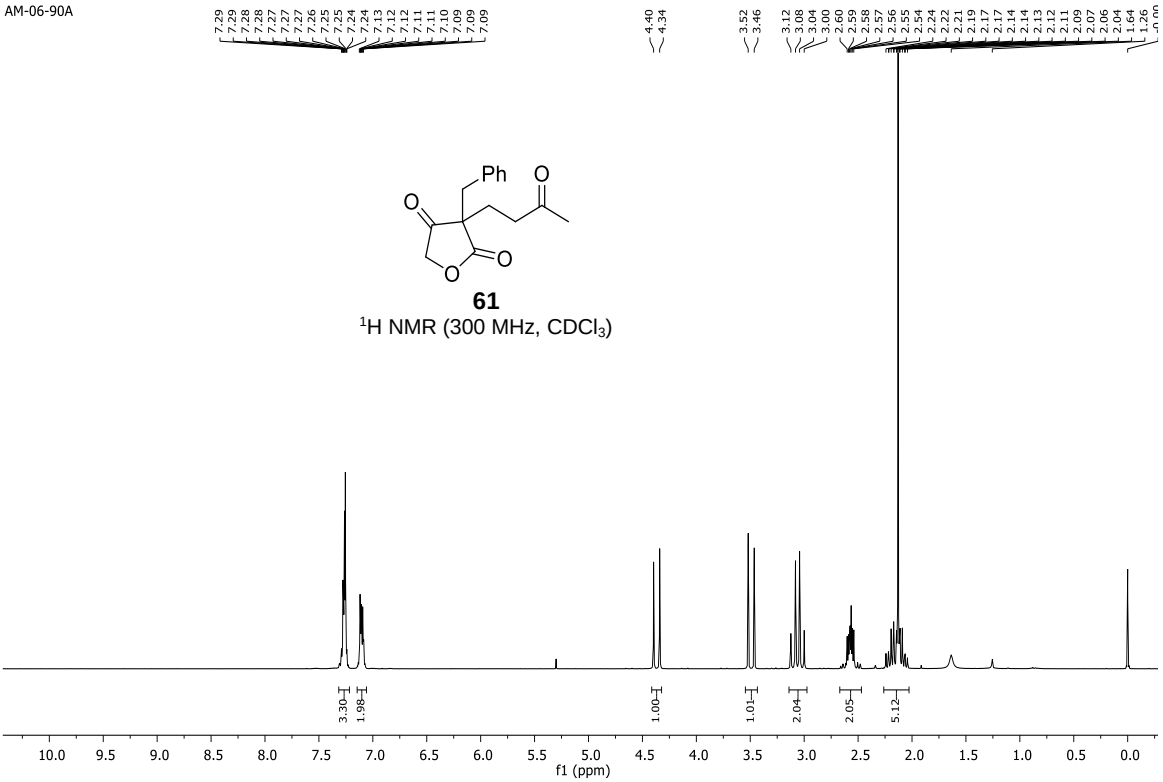
O
O
O
56
13C NMR (75 MHz, CDCl3)
f1 (ppm)

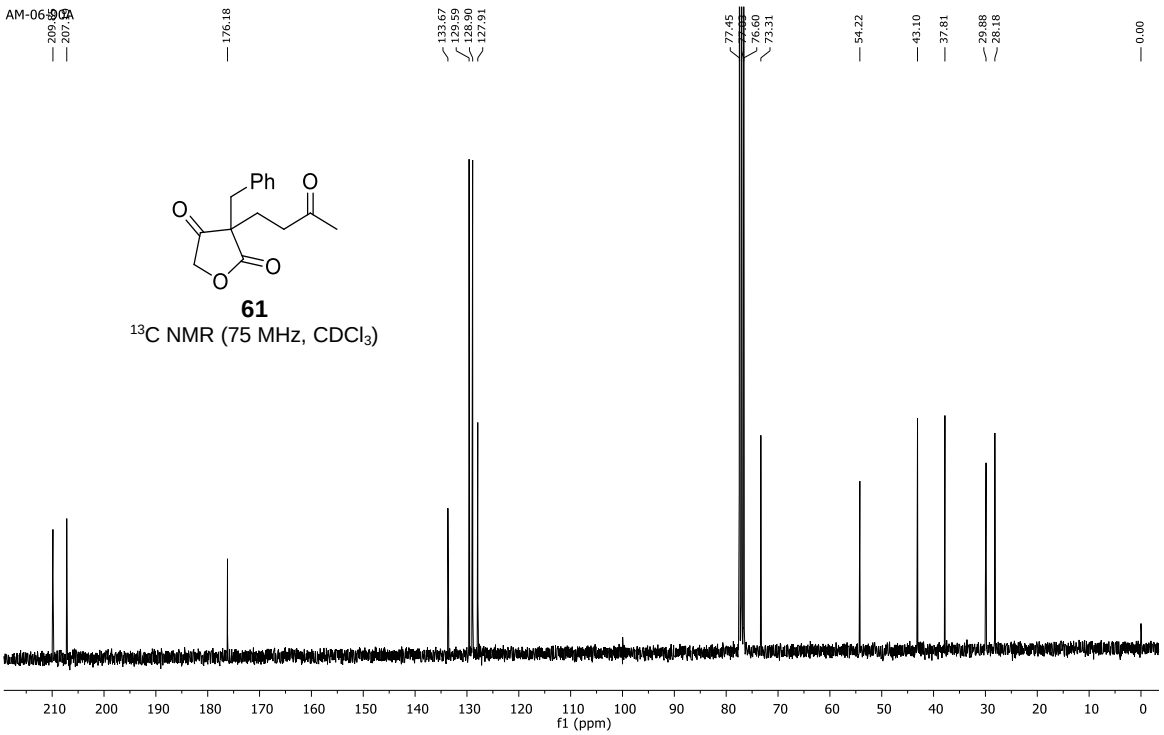

AM-09-27B
HO
O
O
O
59
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-09-27B
HO
O
O
O
59
13C NMR (75 MHz, CDCl3)
f1 (ppm)



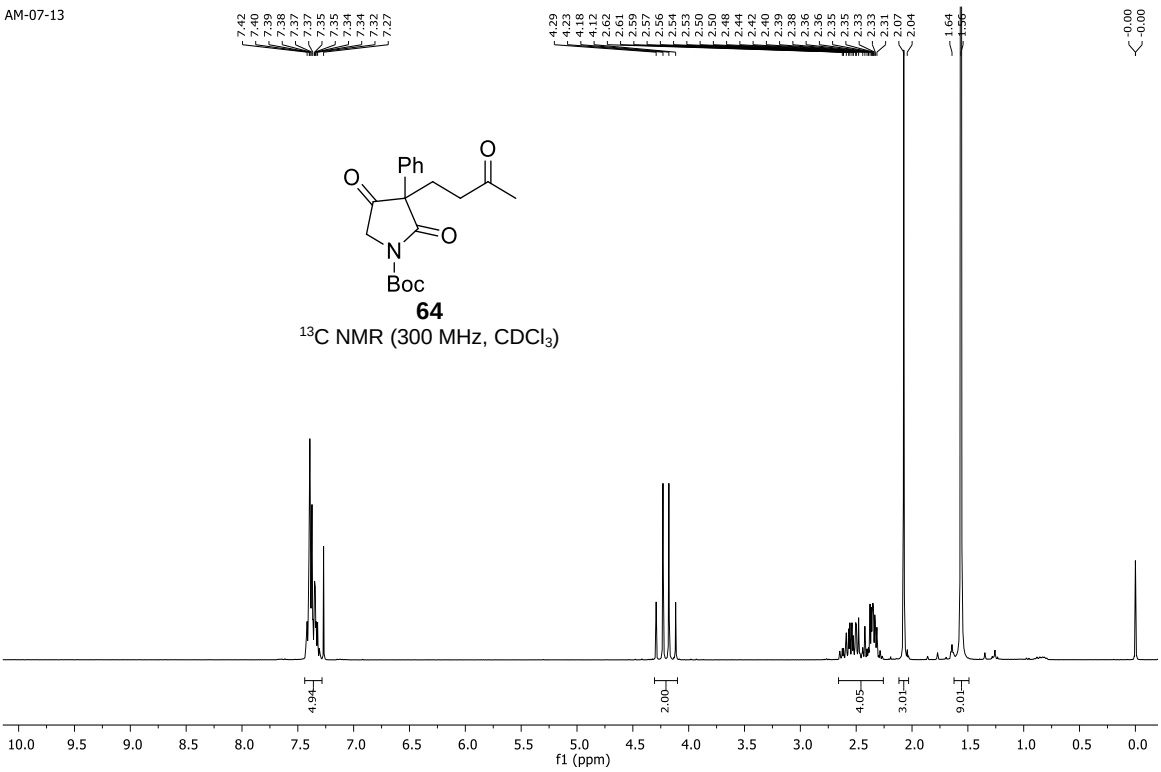
61

^{1}H NMR (300 MHz, $CDCl_3$)



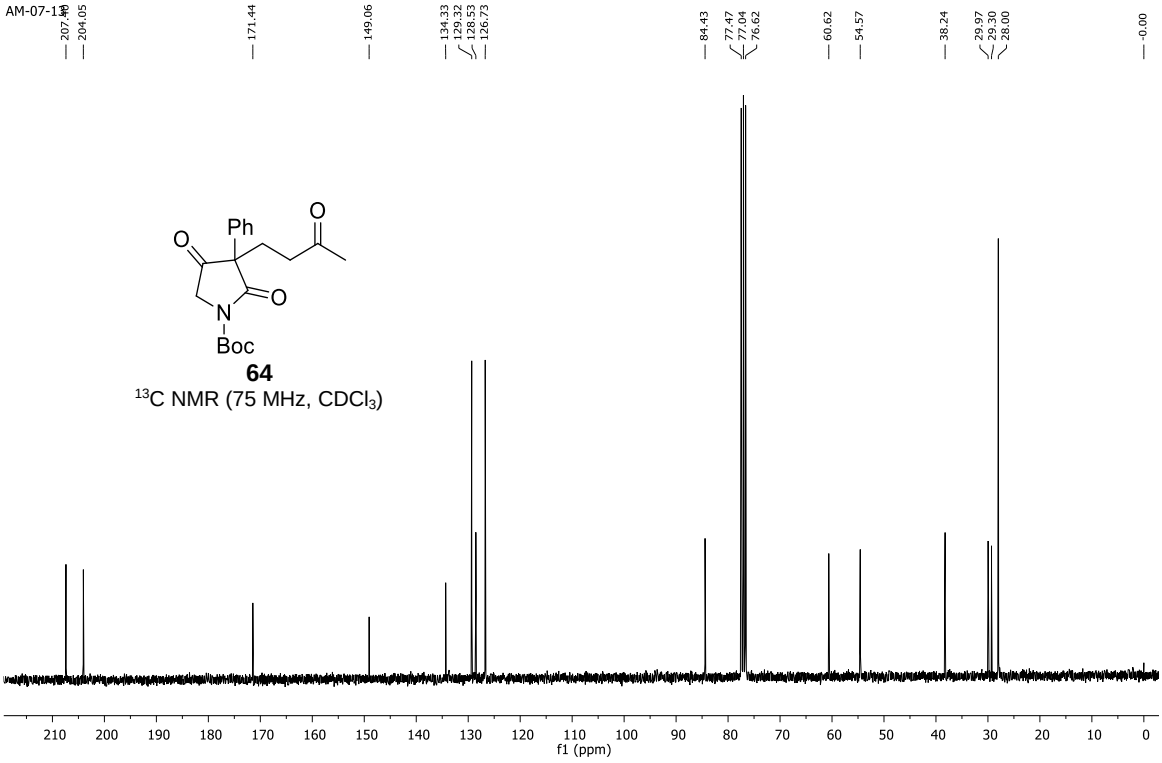
61

^{13}C NMR (75 MHz, $CDCl_3$)



64

^{13}C NMR (300 MHz, $CDCl_3$)



64

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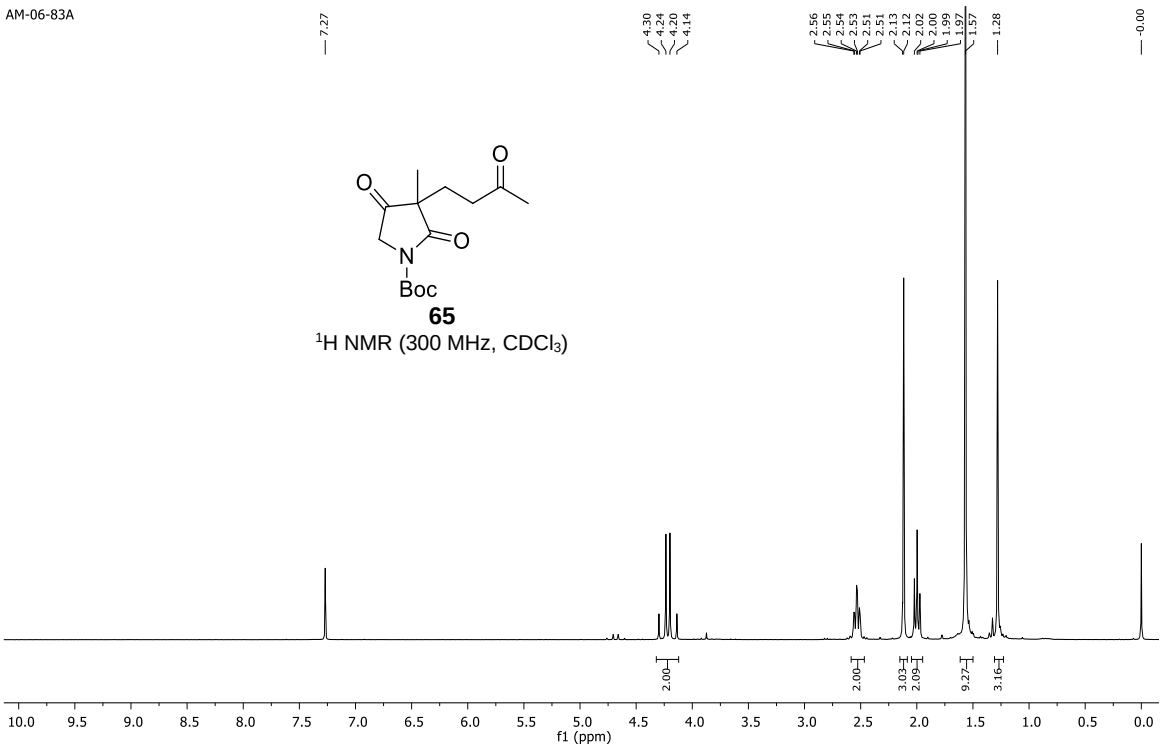
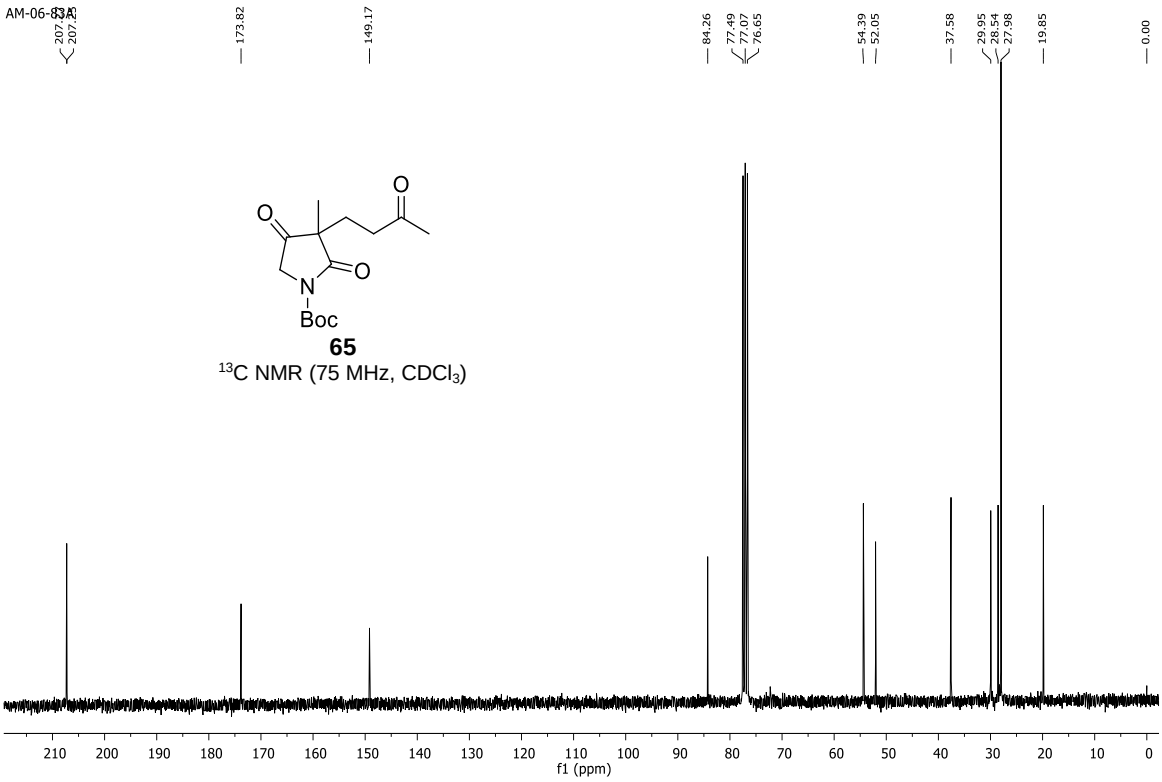


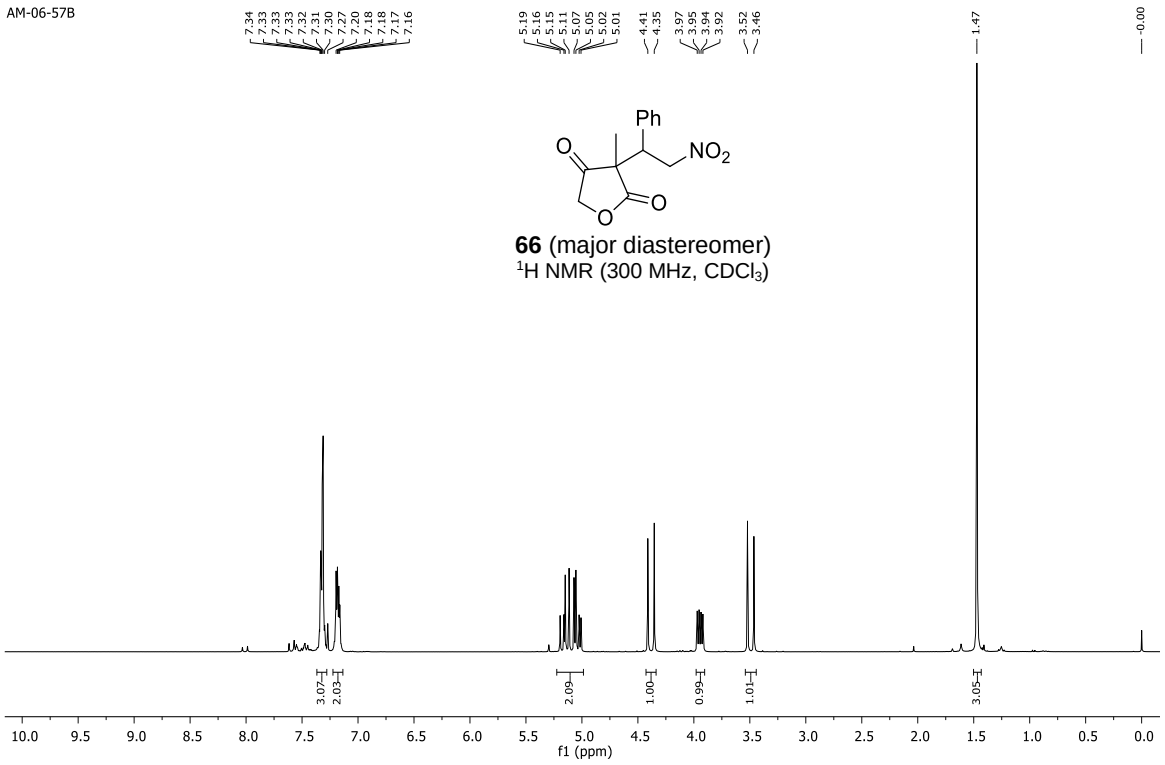
65

^{1}H NMR (300 MHz, $CDCl_3$)

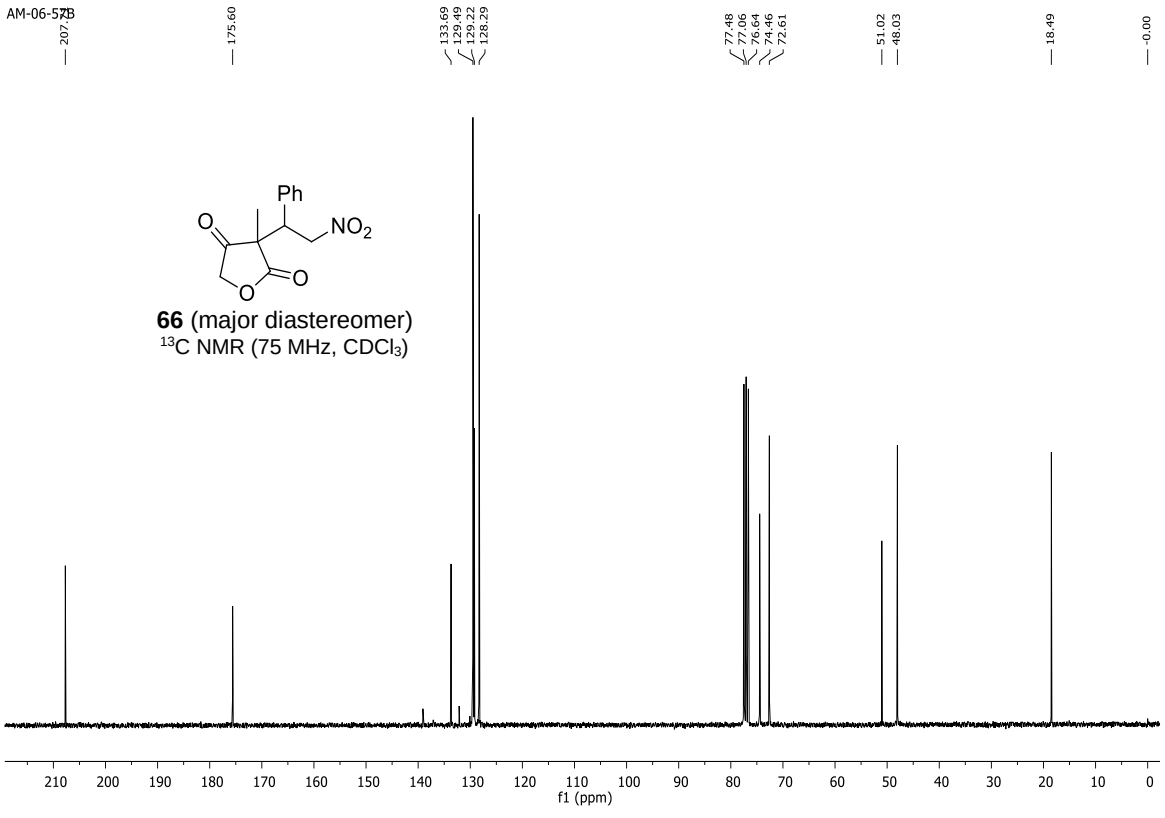


65

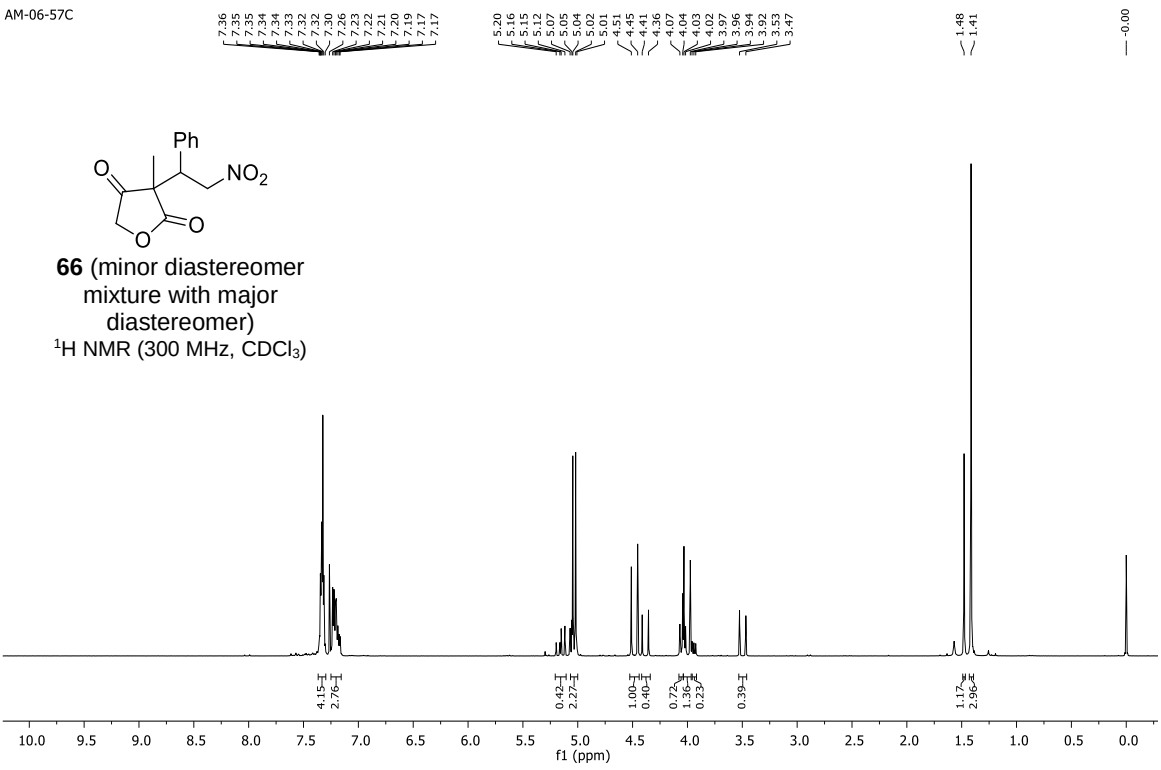
^{13}C NMR (75 MHz, $CDCl_3$)

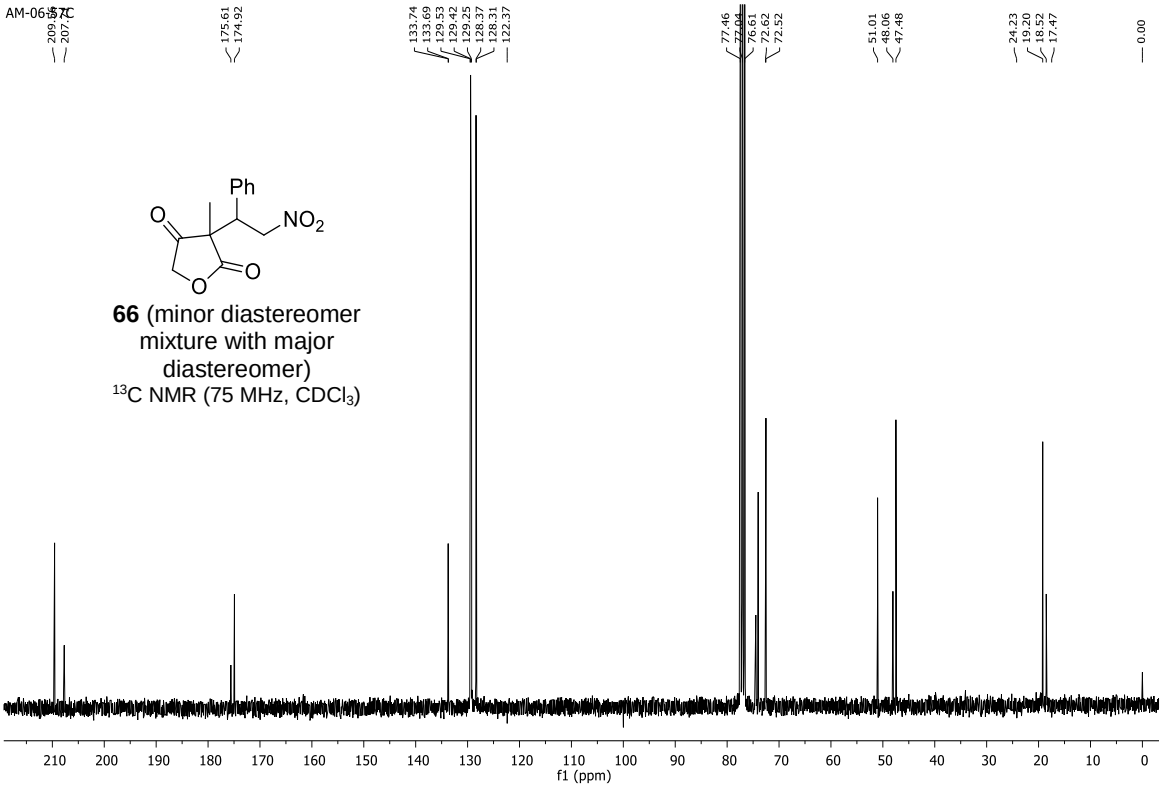


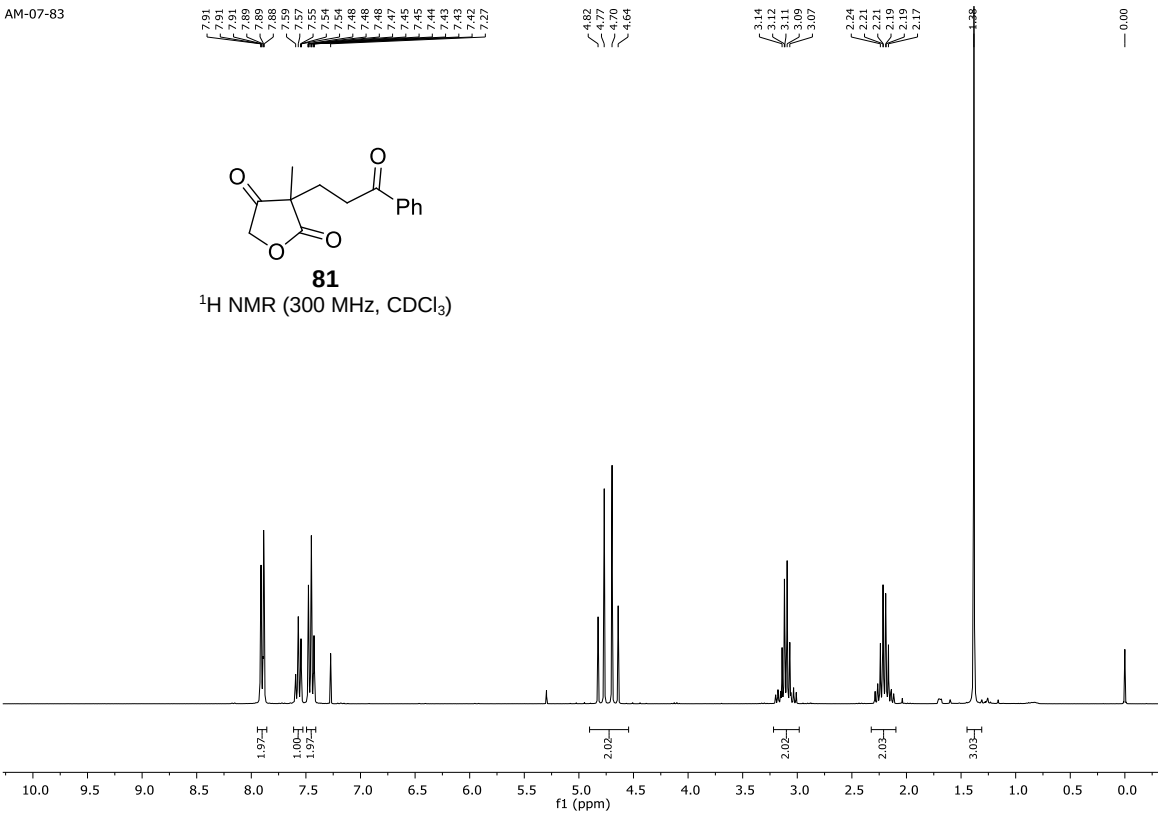
66 (major diastereomer)
^{1}H NMR (300 MHz, $CDCl_3$)



66 (major diastereomer)
^{13}C NMR (75 MHz, $CDCl_3$)

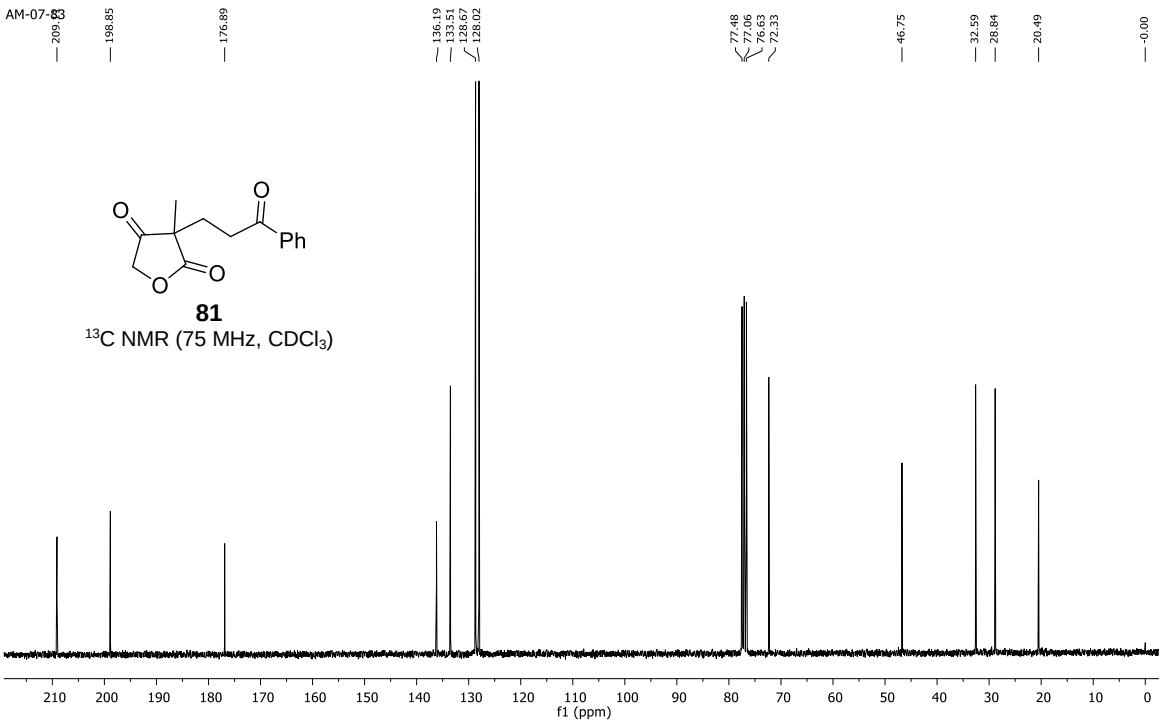

AM-06-57C
Ph
NO2
O
O
O
66 (minor diastereomer mixture with major diastereomer)
1H NMR (300 MHz, CDCl3)
f1 (ppm)


AM-06-57C
Ph
NO2
O
O
O
66 (minor diastereomer mixture with major diastereomer)
13C NMR (75 MHz, CDCl3)
f1 (ppm)



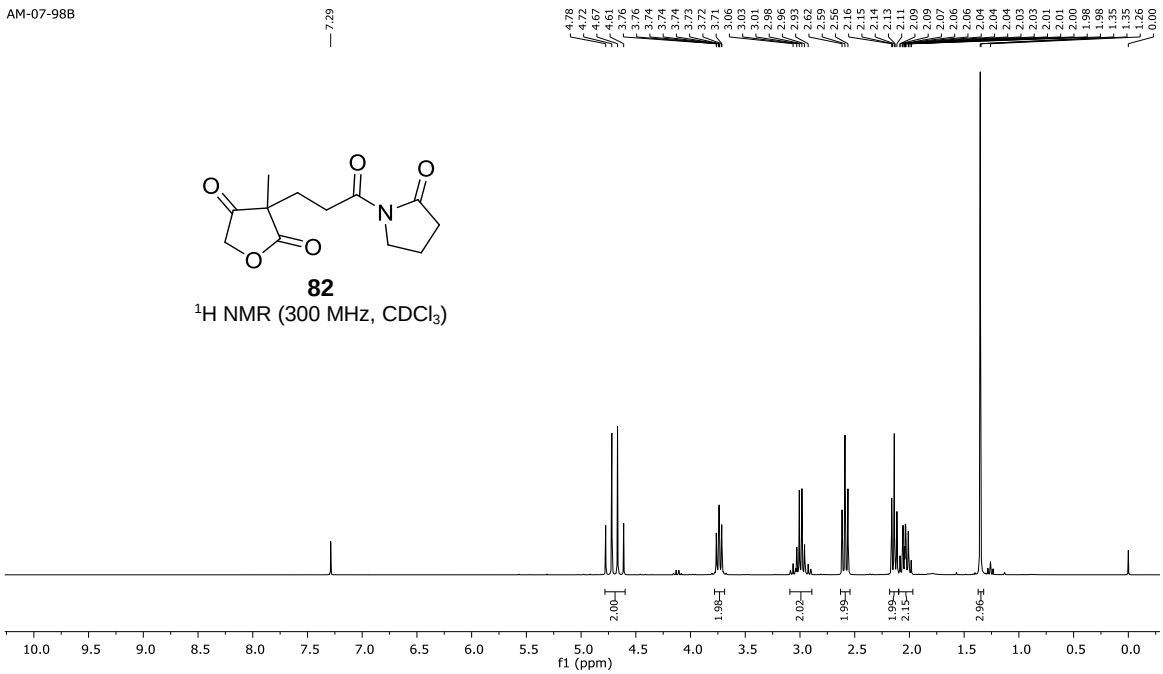
81

^{1}H NMR (300 MHz, $CDCl_3$)



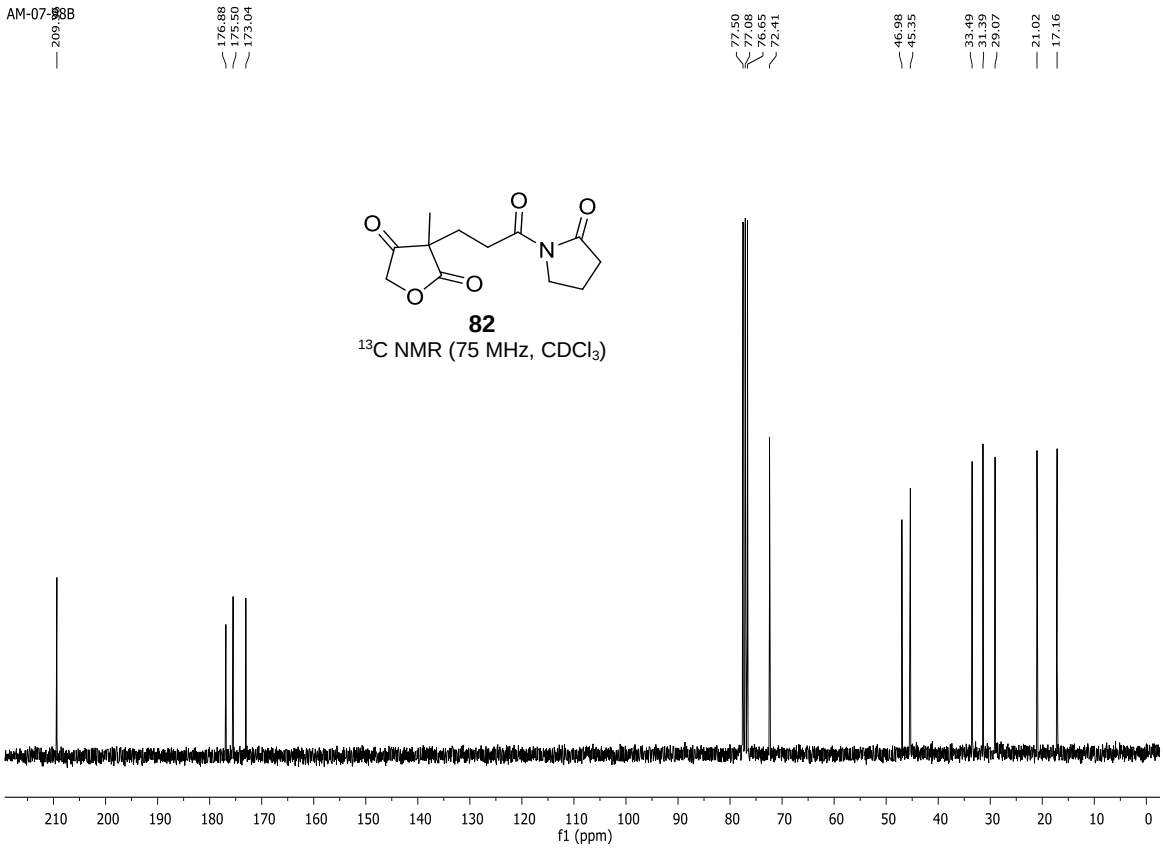
81

^{13}C NMR (75 MHz, $CDCl_3$)



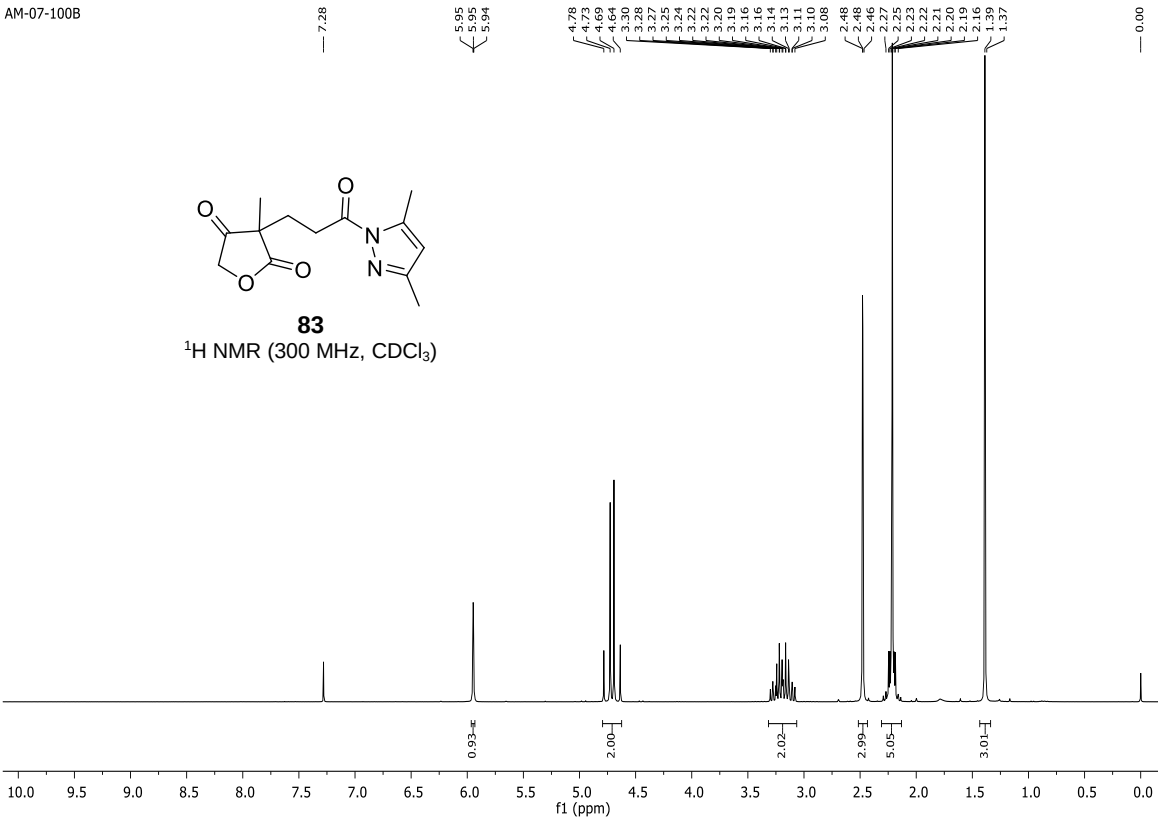
82

^{1}H NMR (300 MHz, $CDCl_3$)



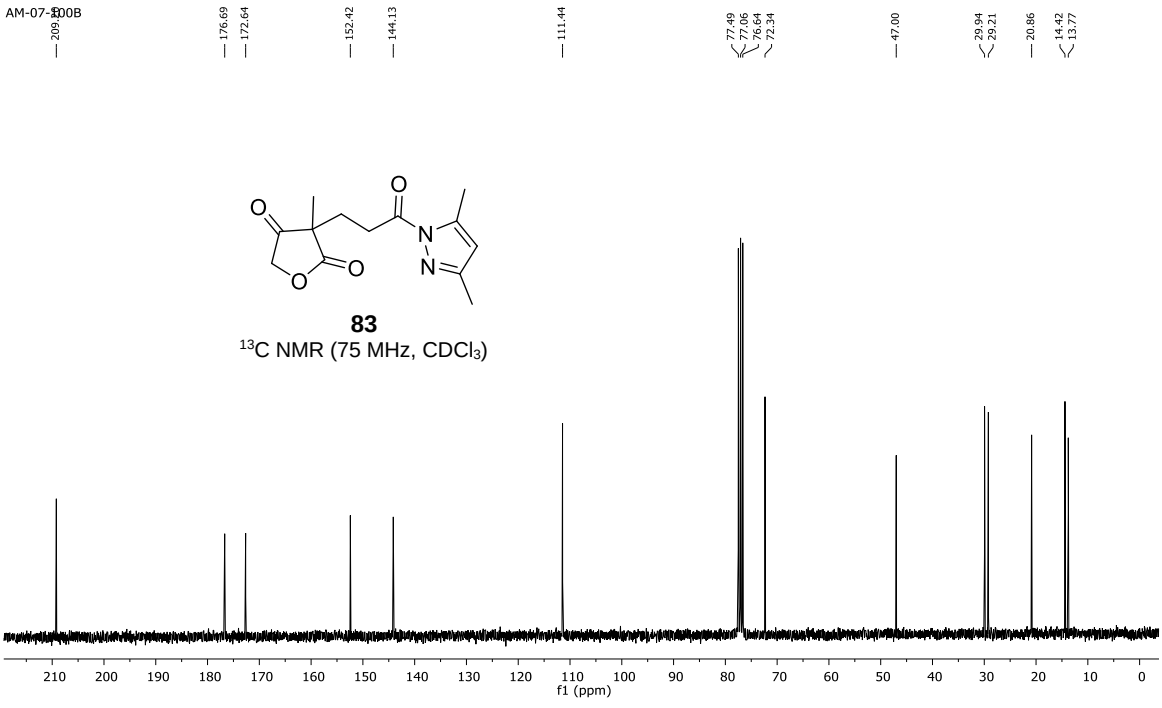
82

^{13}C NMR (75 MHz, $CDCl_3$)



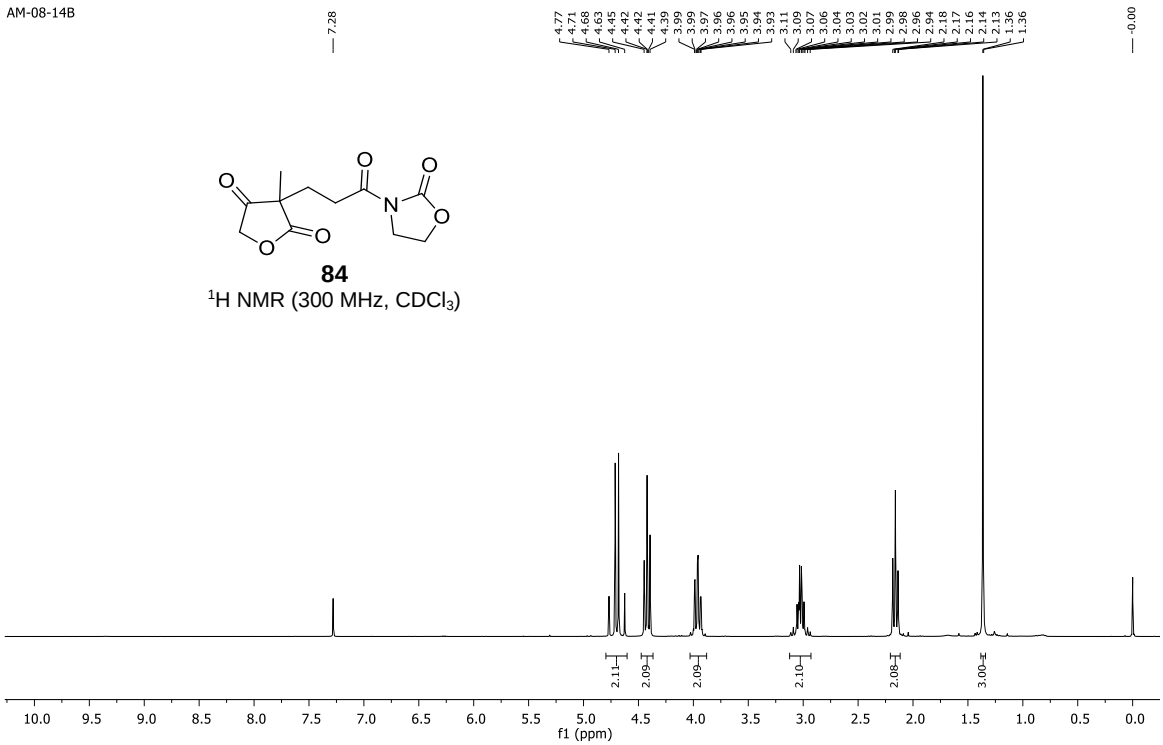
83

^{1}H NMR (300 MHz, $CDCl_3$)



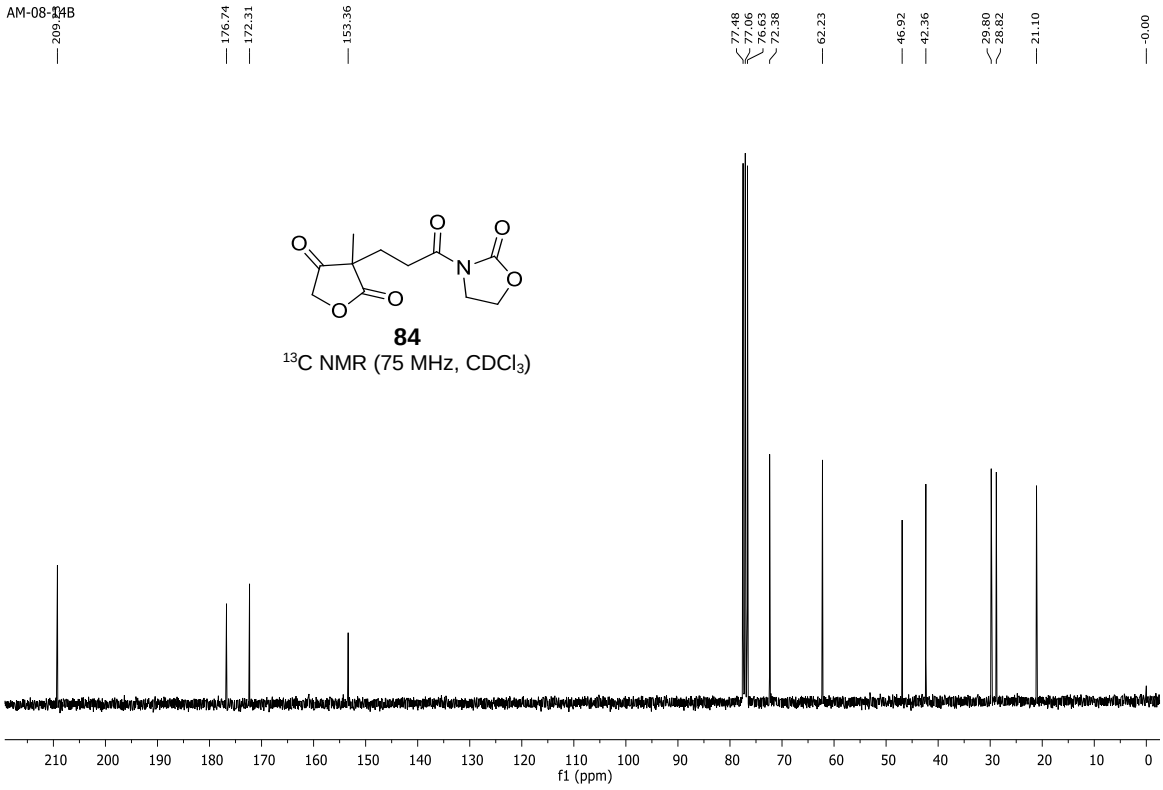
83

^{13}C NMR (75 MHz, $CDCl_3$)



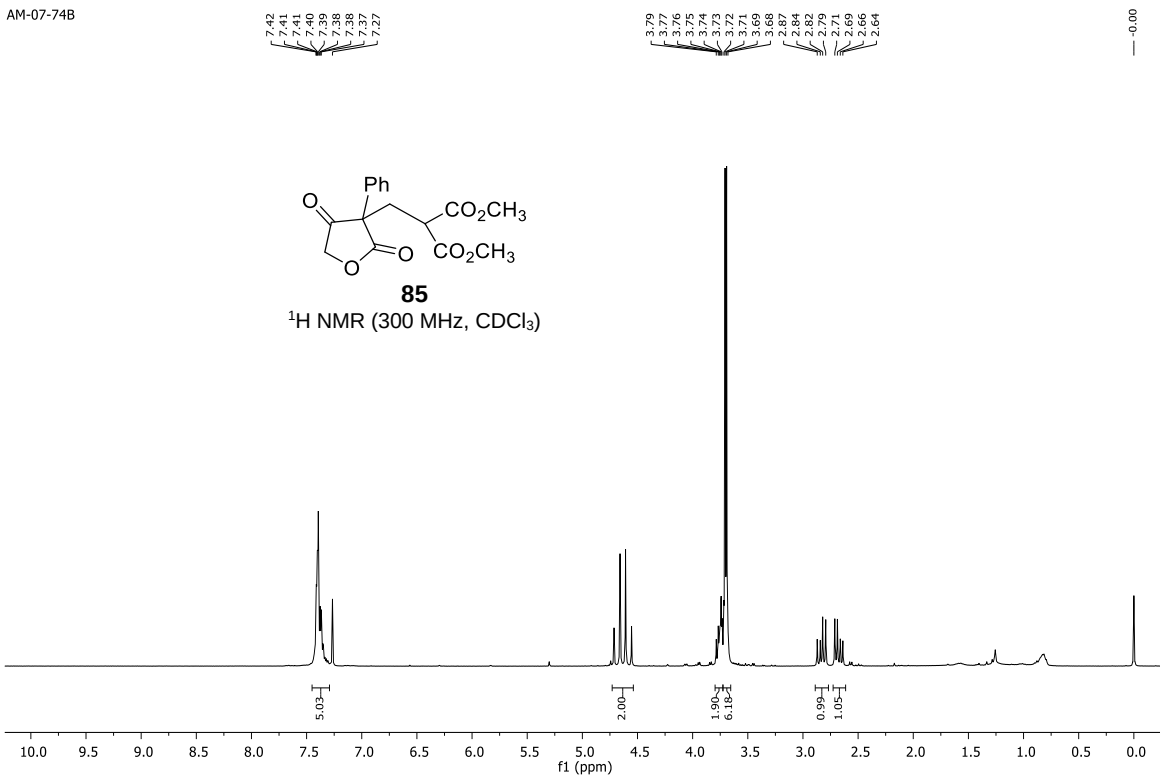
84

^{1}H NMR (300 MHz, $CDCl_3$)



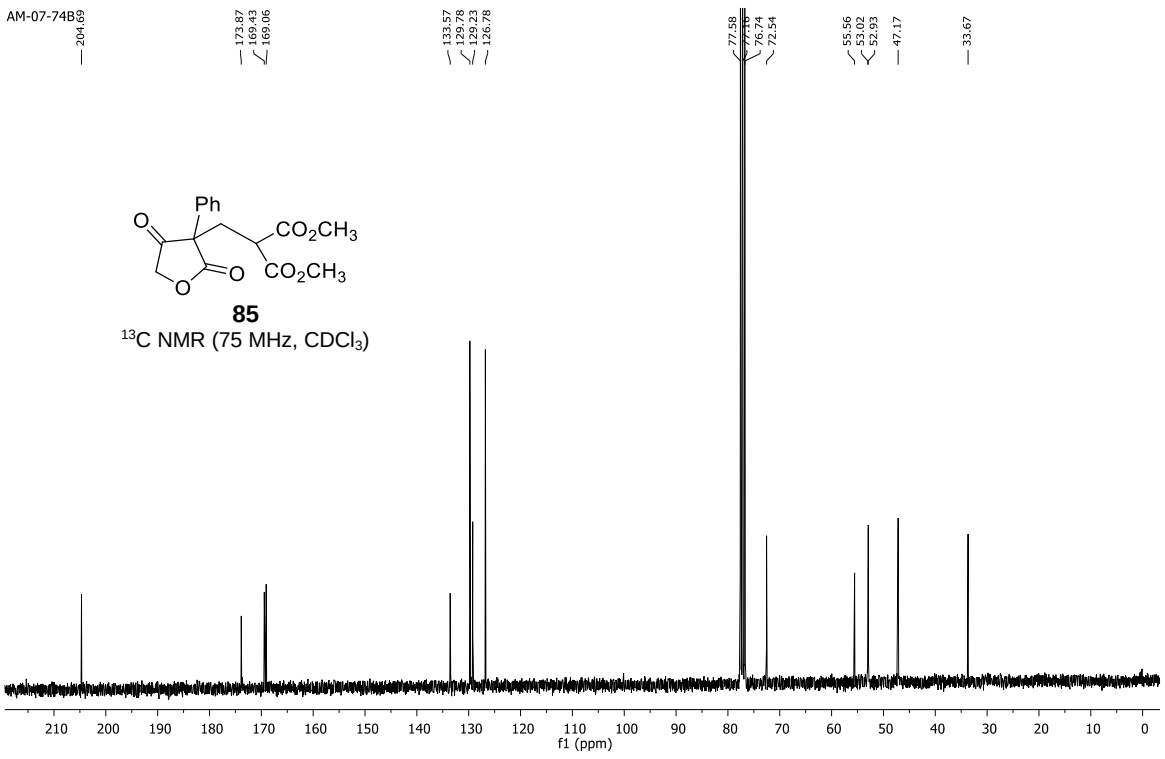
84

^{13}C NMR (75 MHz, $CDCl_3$)



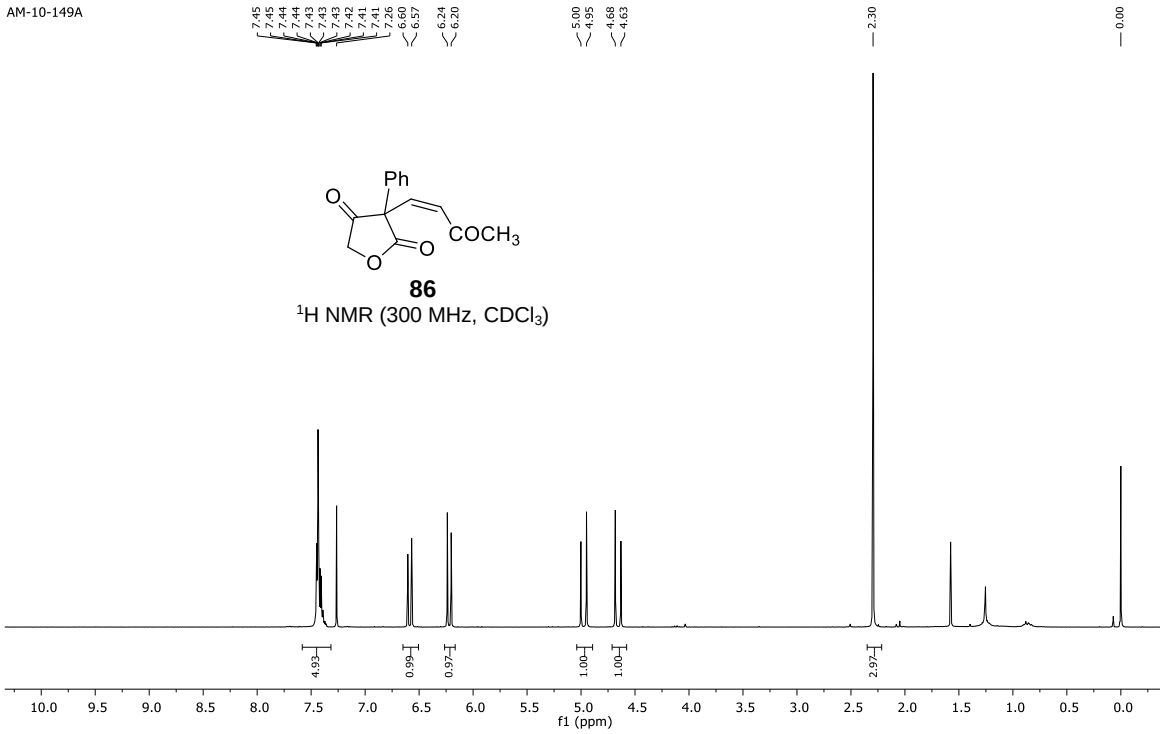
85

^{1}H NMR (300 MHz, $CDCl_3$)



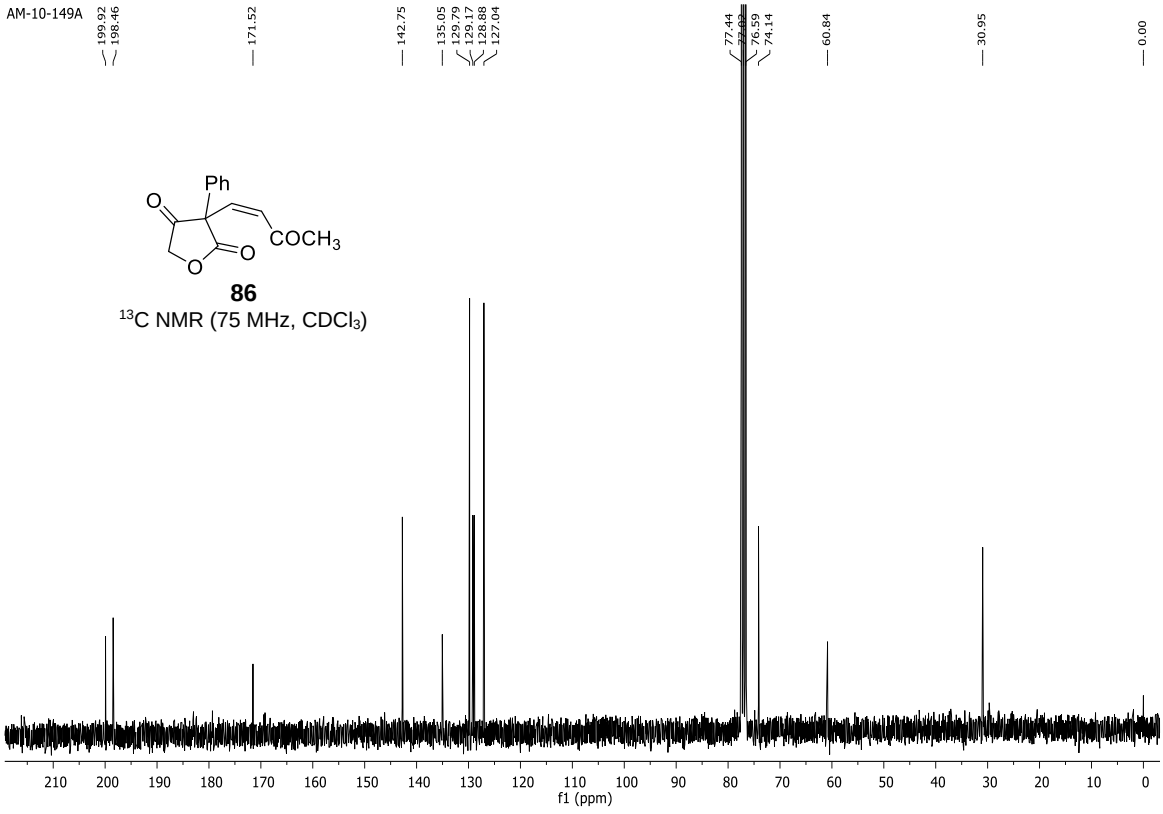
85

^{13}C NMR (75 MHz, $CDCl_3$)



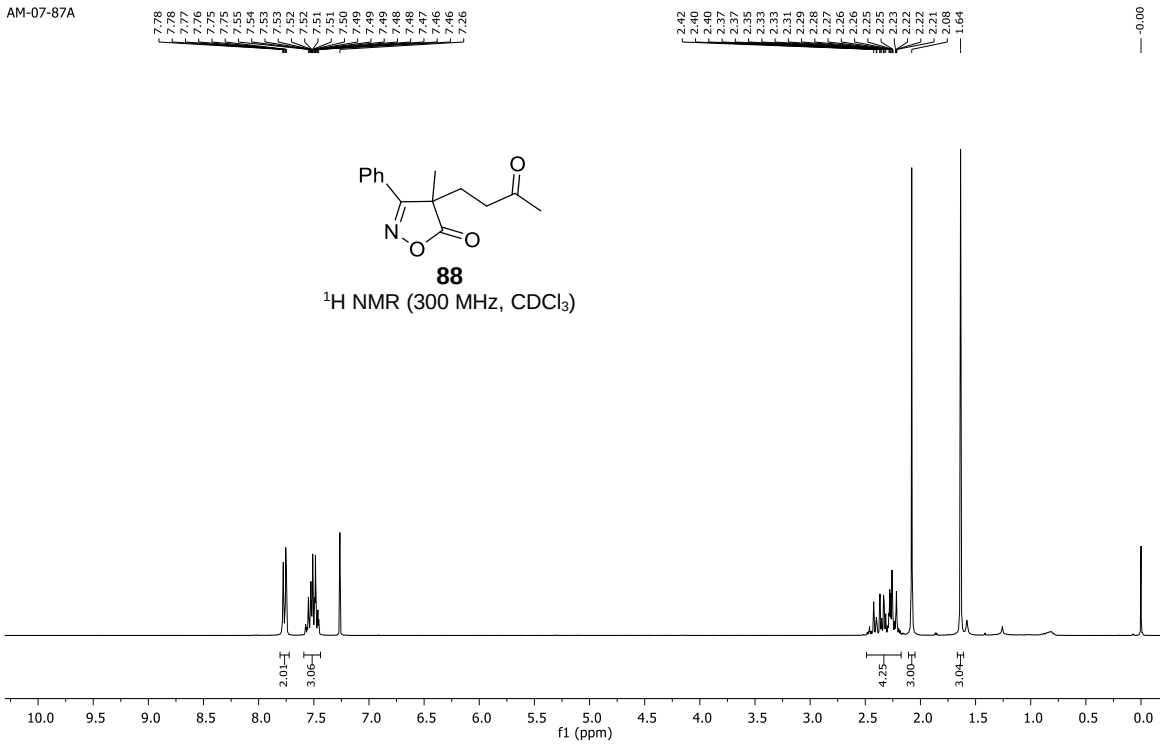
86

^{1}H NMR (300 MHz, $CDCl_3$)



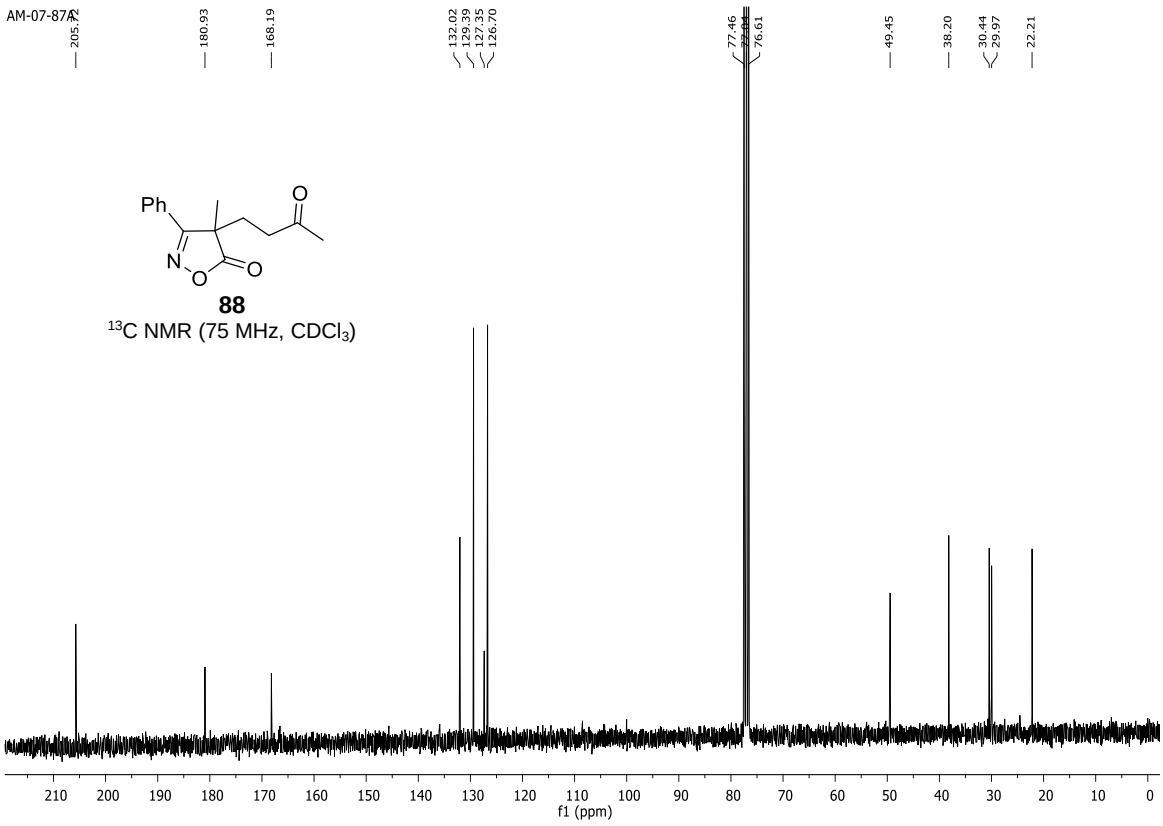
86

^{13}C NMR (75 MHz, $CDCl_3$)



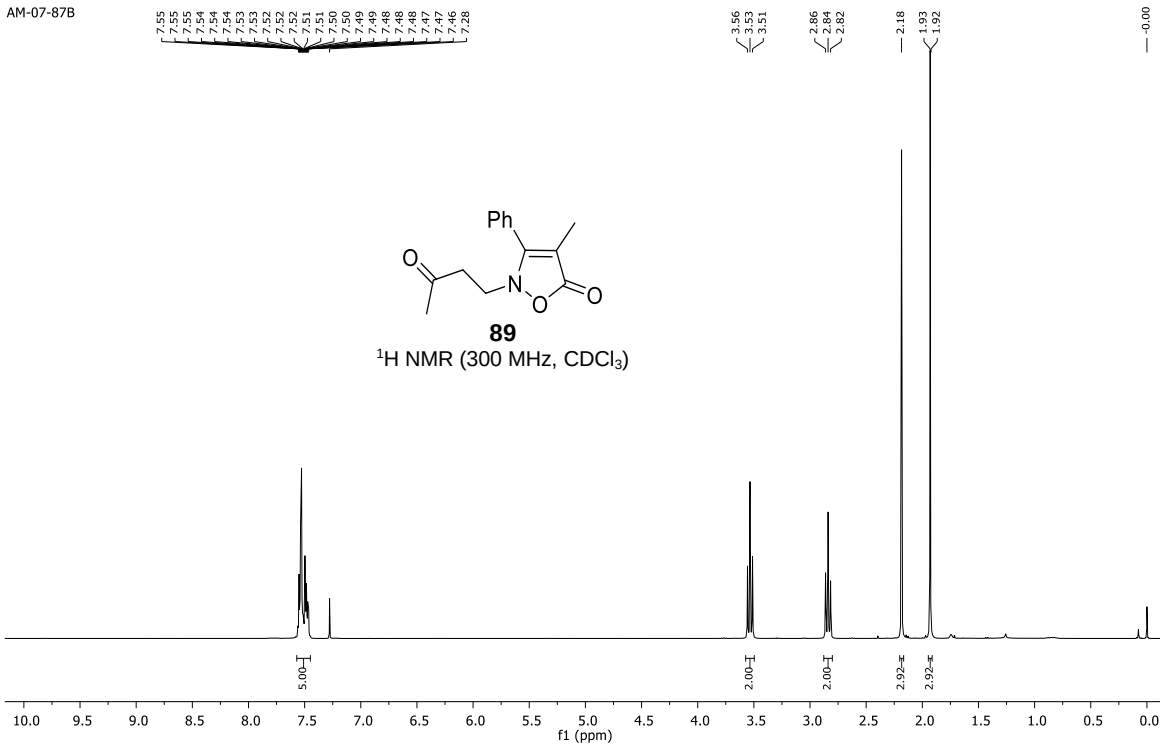
88

^{1}H NMR (300 MHz, $CDCl_3$)



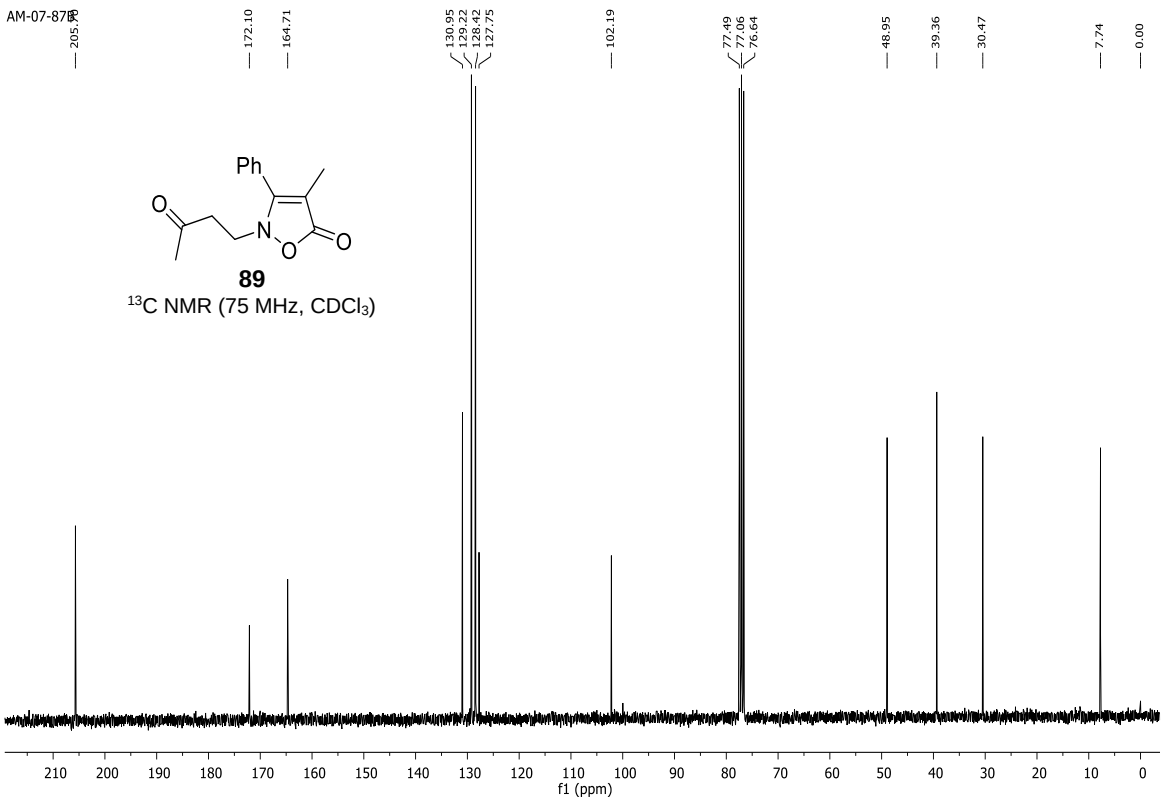
88

^{13}C NMR (75 MHz, $CDCl_3$)



89

^{1}H NMR (300 MHz, $CDCl_3$)



89

^{13}C NMR (75 MHz, $CDCl_3$)

2.9 Selected HPLC traces

Memorial University

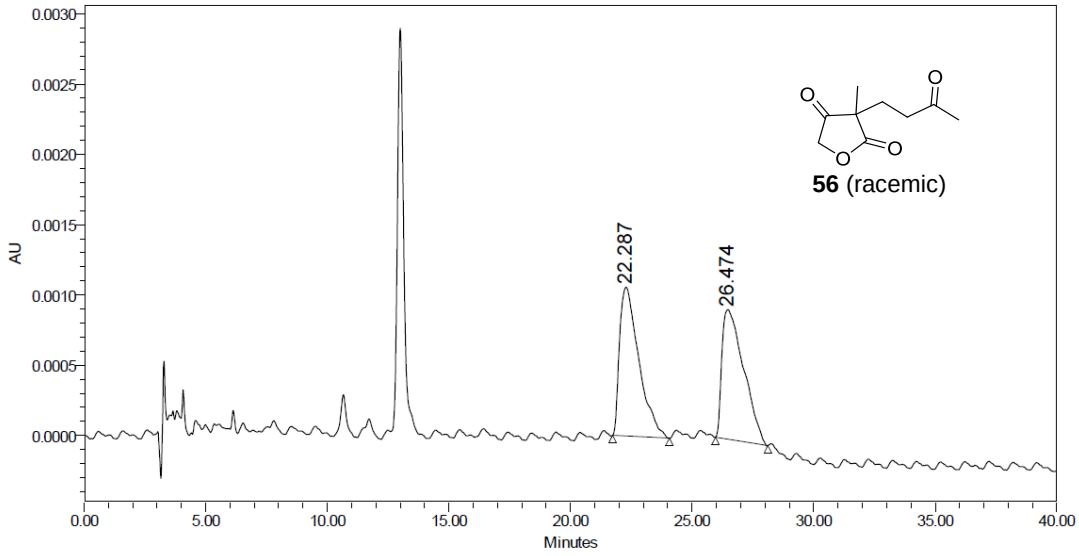
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-06-68A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	15/09/2015 2:41:16 PM NDT
Vial:	1	Acq. Method:	AS_H 80Hex20IPA
Injection #:	1	Date Processed:	11/12/2017 4:38:54 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



56 (racemic)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	22.287	58343	50.46	1058	53.47
2	26.474	57273	49.54	921	46.53

Report Method: Individual Control Report

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Printed: 11/12/2017

4:39:31 PM Canada/Newfoundland

Memorial University

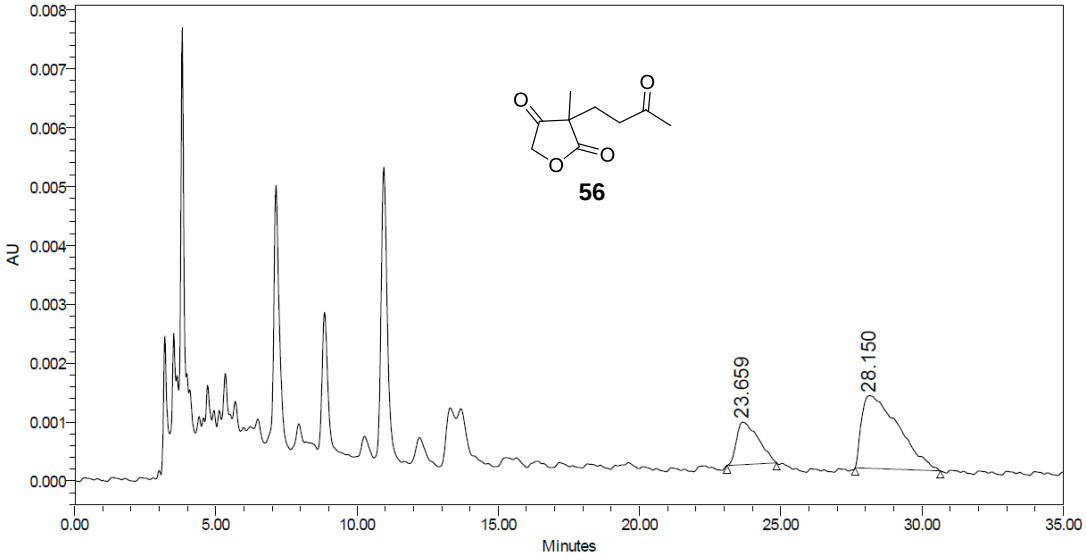
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-06-73A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	27/09/2015 5:54:57 PM NDT
Vial:	1	Acq. Method:	AS_H 80Hex20IPA
Injection #:	1	Date Processed:	27/09/2015 6:33:23 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	35.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	23.659	38480	25.47	723	36.95
2	28.150	112599	74.53	1234	63.05

Report Method: Individual Control Report

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Printed: 07/12/2017

5:36:22 PM Canada/Newfoundland

Memorial University

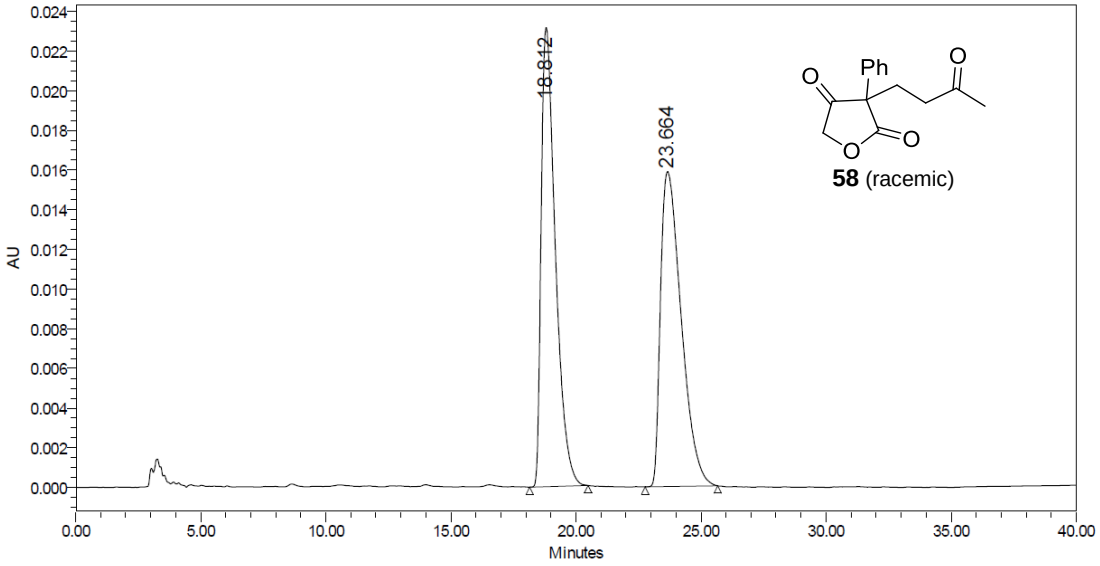
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-32	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	19/11/2015 3:27:50 PM NST
Vial:	1	Acq. Method:	AS_H 80%Hex20%IPA2
Injection #:	1	Date Processed:	19/11/2015 4:14:54 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



58 (racemic)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.812	911699	50.02	23144	59.32
2	23.664	910966	49.98	15870	40.68

Report Method: Individual Control Report

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Printed: 19/11/2015

4:15:17 PM Canada/Newfoundland

Memorial University

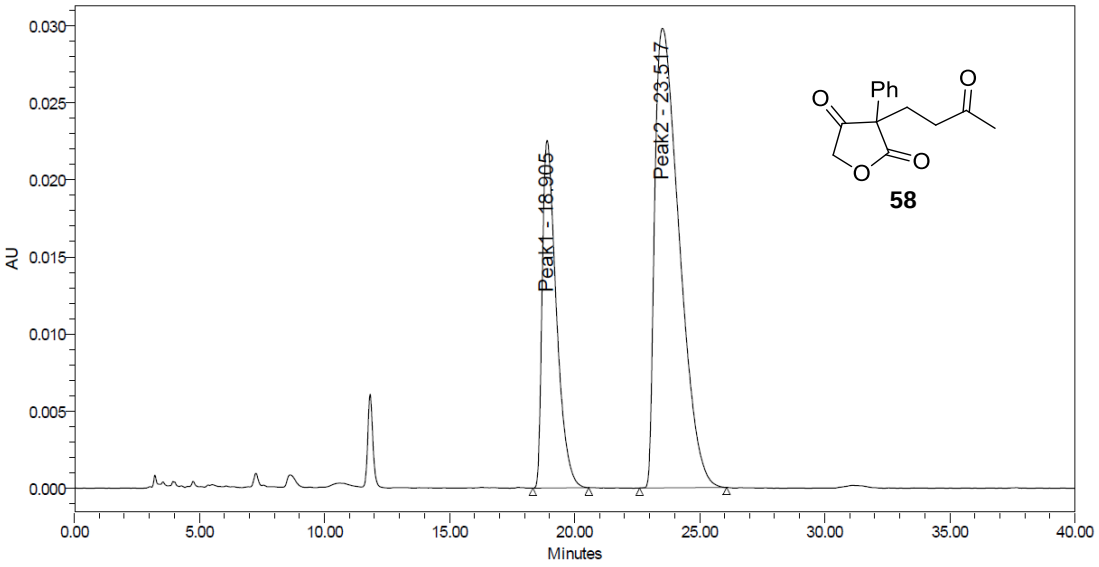
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-25	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	19/11/2015 4:51:41 PM NST
Vial:	1	Acq. Method:	AS_H 80%Hex20%IPA2
Injection #:	1	Date Processed:	19/11/2015 6:38:53 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	18.905	883772	30.36	22559	43.08
2	Peak2	23.517	2027465	69.64	29806	56.92

Memorial University

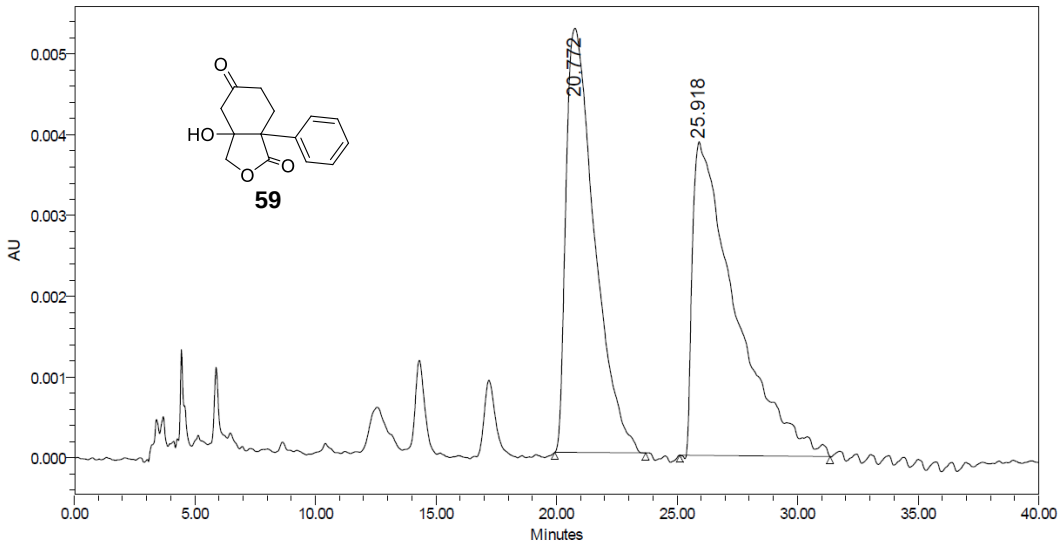
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-10-107B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	12/12/2016 2:47:03 PM NST
Vial:	1	Acq. Method:	AS_H 70Hex30IPA
Injection #:	1	Date Processed:	12/12/2016 3:32:40 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	20.772	431875	47.28	5249	57.49
2	25.918	481507	52.72	3881	42.51

Memorial University

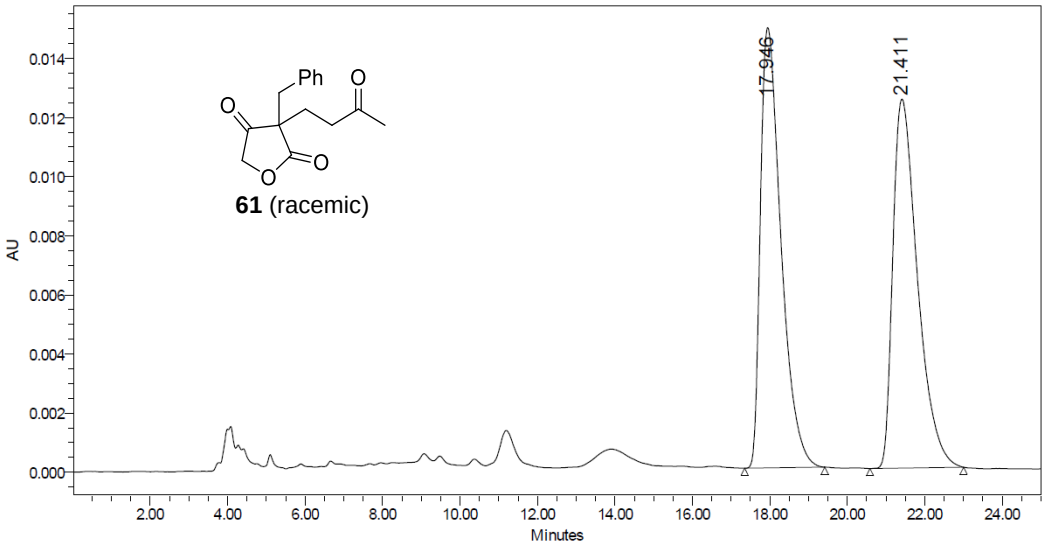
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-30	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	18/11/2015 8:34:27 PM NST
Vial:	1	Acq. Method:	AS_H 80%Hex20%IPA1
Injection #:	1	Date Processed:	18/11/2015 9:12:16 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	25.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.946	549874	49.93	14895	54.40
2	21.411	551366	50.07	12484	45.60

Memorial University

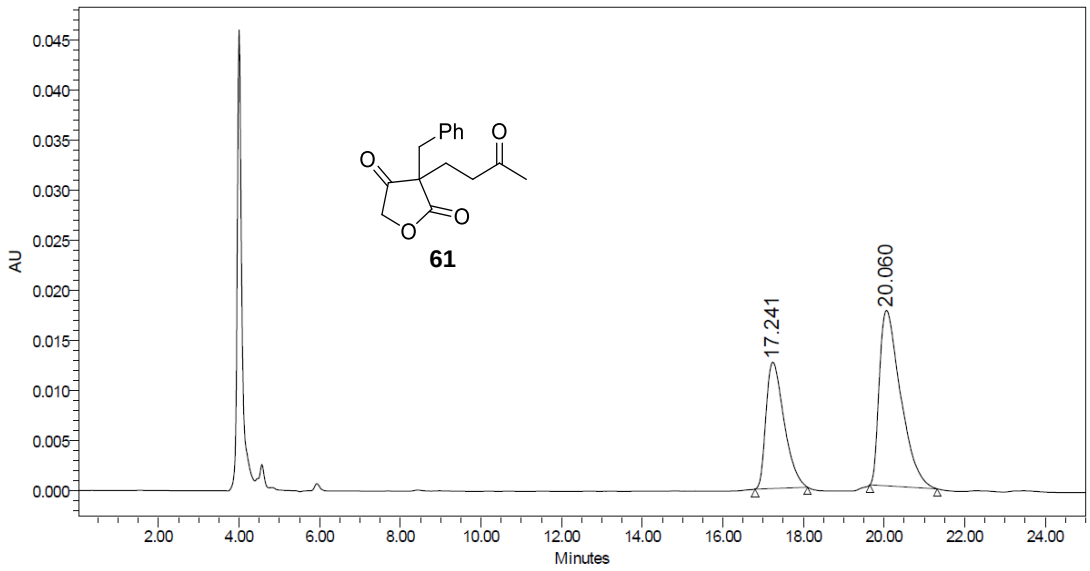
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-44	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	02/12/2015 12:37:36 PM NST
Vial:	1	Acq. Method:	AS_H 80%Hex20%IPA1
Injection #:	1	Date Processed:	02/12/2015 1:28:53 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	25.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



61

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.241	393286	37.90	12610	41.86
2	20.060	644273	62.10	17515	58.14

Report Method: Individual Control Report

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Printed: 07/12/2017

5:33:03 PM Canada/Newfoundland

Memorial University

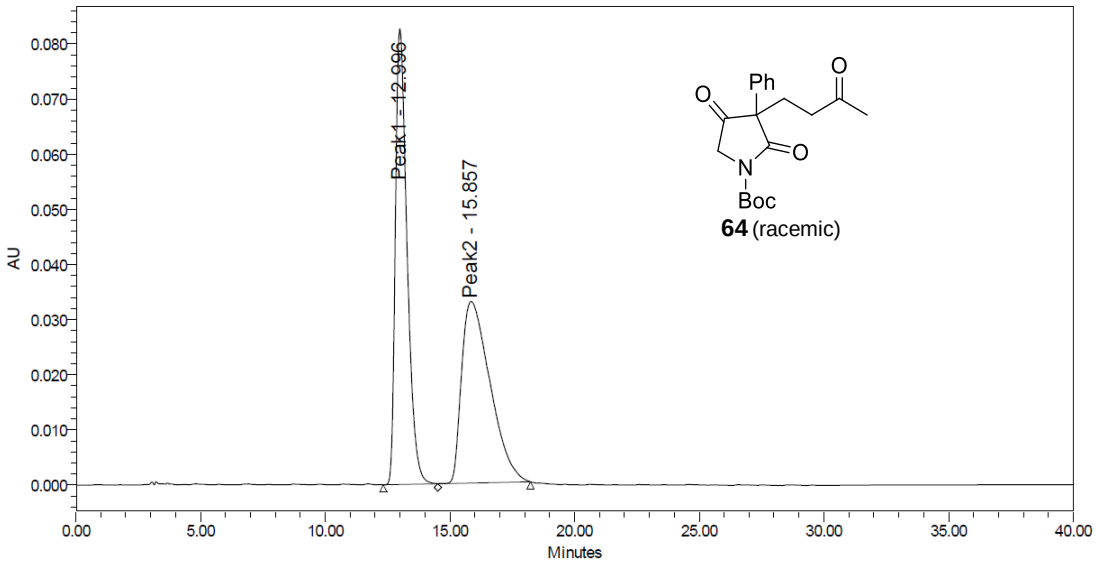
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-12	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	03/11/2015 10:45:23 AM NST
Vial:	1	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	03/11/2015 11:27:41 AM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



64 (racemic)

	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	12.996	2682164	50.61	82600	71.53
2	Peak2	15.857	2617760	49.39	32884	28.47

Memorial University

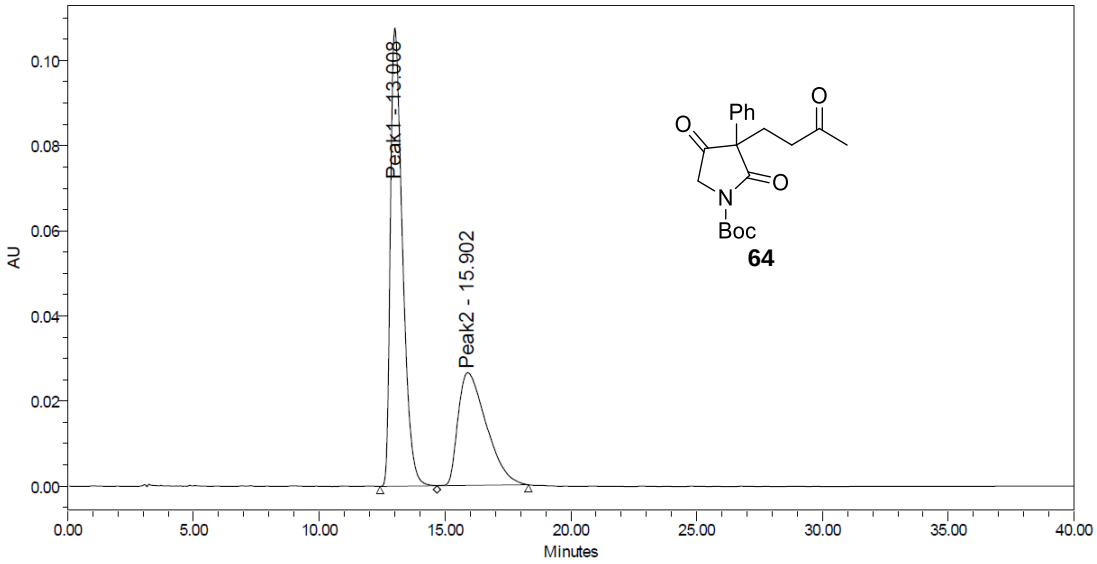
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-13	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	03/11/2015 12:04:09 PM NST
Vial:	1	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	03/11/2015 12:45:29 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	13.008	3584212	63.44	107735	80.26
2	Peak2	15.902	2065527	36.56	26495	19.74

Report Method: Individual Control Report

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Printed: 03/11/2015 12:46:27 PM Canada/Newfoundland

Memorial University

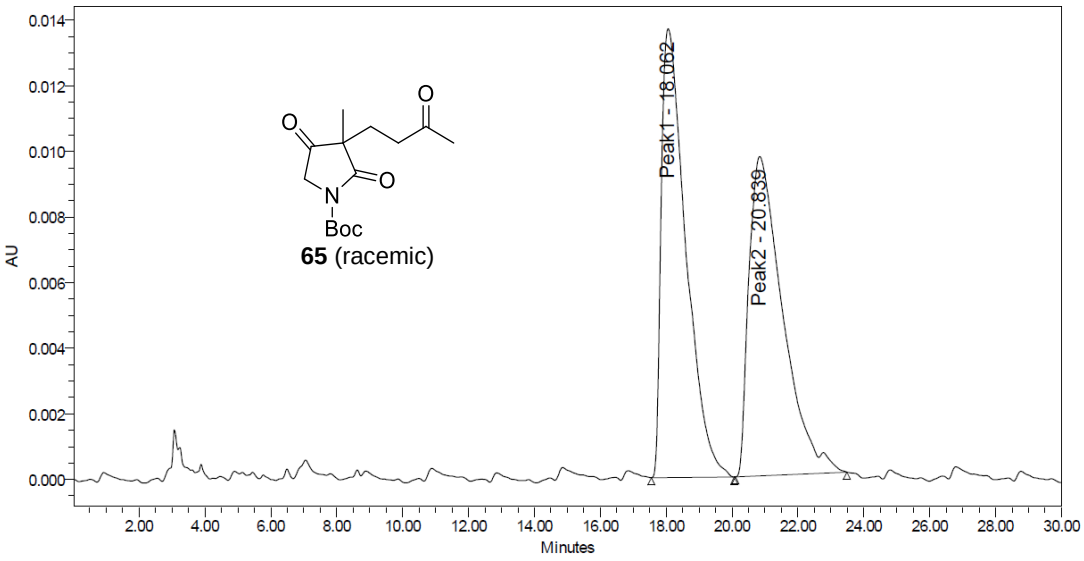
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-06-82	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	13/10/2015 7:59:13 PM NDT
Vial:	1	Acq. Method:	AS_H95Hex5IPA
Injection #:	1	Date Processed:	13/10/2015 8:33:44 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



65 (racemic)

	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	18.062	709939	50.65	13682	58.43
2	Peak2	20.839	691606	49.35	9734	41.57

Report Method: Individual Control Report

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Memorial University

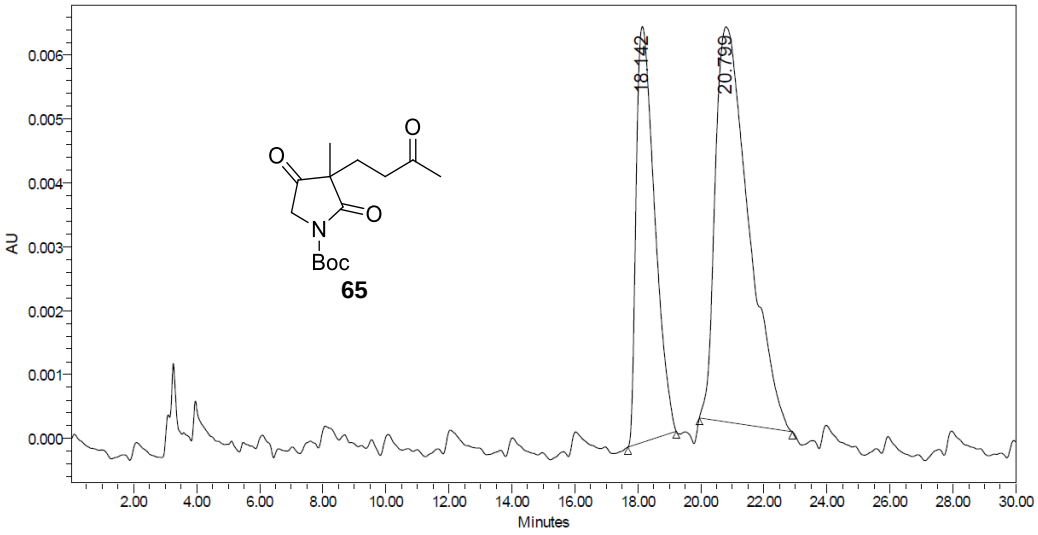
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-06-83A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	13/10/2015 8:58:10 PM NDT
Vial:	1	Acq. Method:	AS_H95Hex5IPA
Injection #:	1	Date Processed:	13/10/2015 9:30:07 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.142	265373	36.84	6513	51.30
2	20.799	455045	63.16	6183	48.70

Report Method: Individual Control Report

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Printed: 13/10/2015

9:31:40 PM Canada/Newfoundland

Memorial University

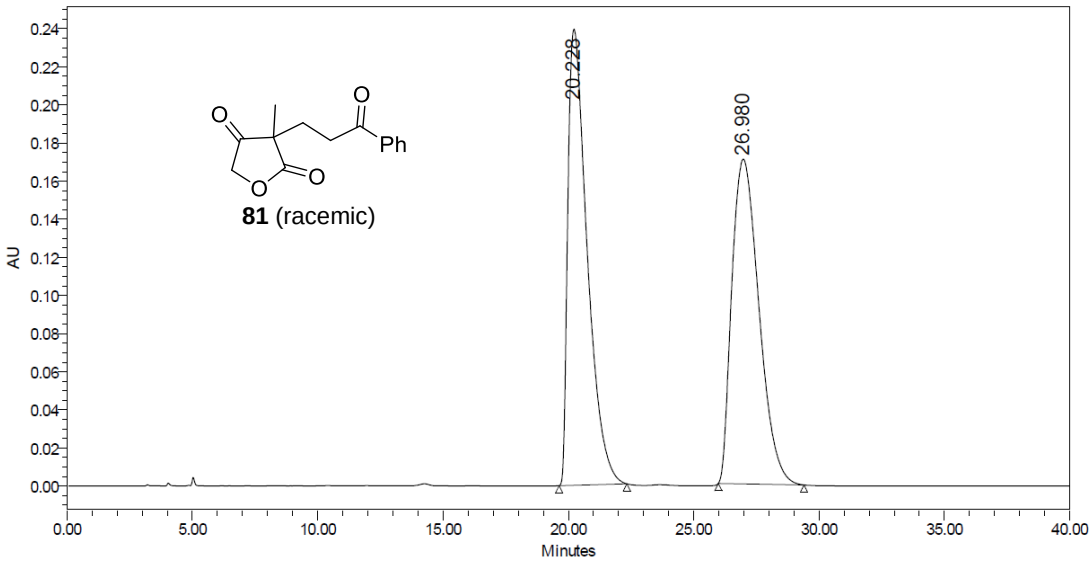
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-07-84	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/01/2016 3:39:54 PM NST
Vial:	1	Acq. Method:	AS_H 80%Hex20%IPA2
Injection #:	1	Date Processed:	11/01/2016 4:46:30 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	20.228	12817375	50.04	239400	58.41
2	26.980	12794496	49.96	170433	41.59

Report Method: Individual Control Report

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5:11:38 PM Canada/Newfoundland

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Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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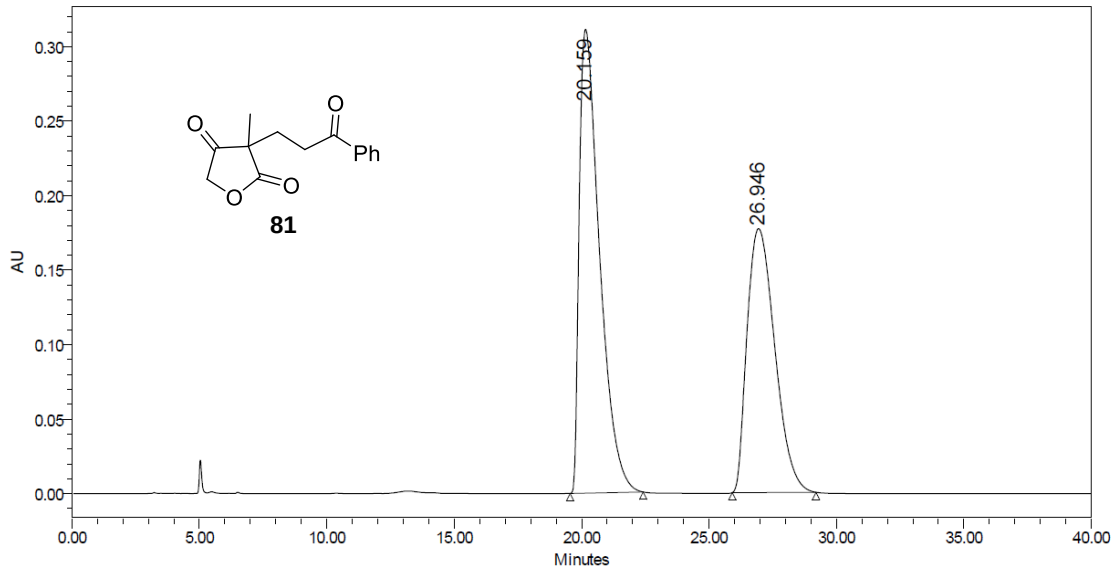

81

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1	20.159	17263792	56.31	311207	63.74
2	26.946	13395933	43.69	177028	36.26

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Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Injection #:	1	Date Processed:	02/02/2016 3:18:48 PM NST
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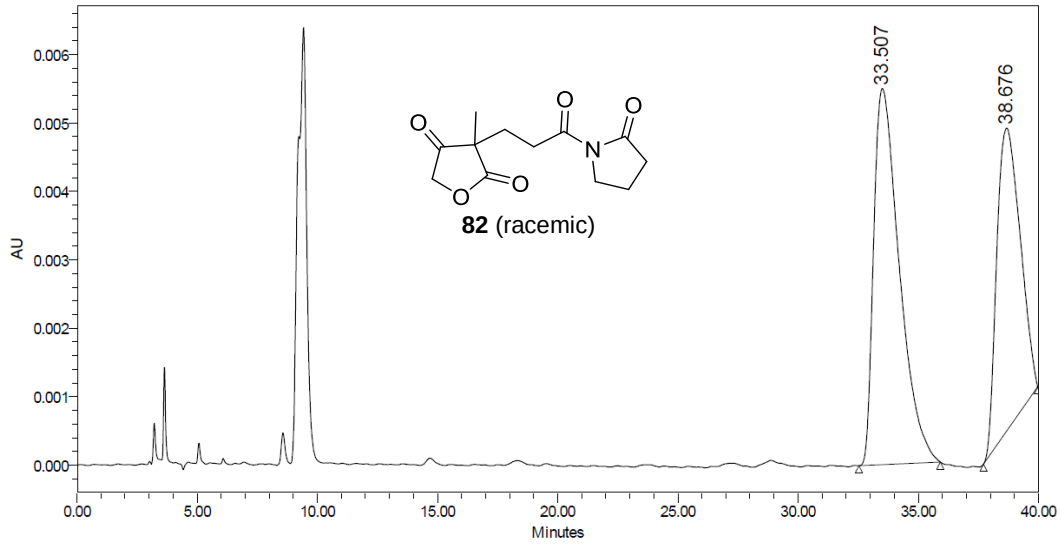

82 (racemic)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	33.507	408560	57.75	5498	55.37
2	38.676	298871	42.25	4432	44.63

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Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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Injection #:	1	Date Processed:	02/02/2016 7:49:08 PM NST
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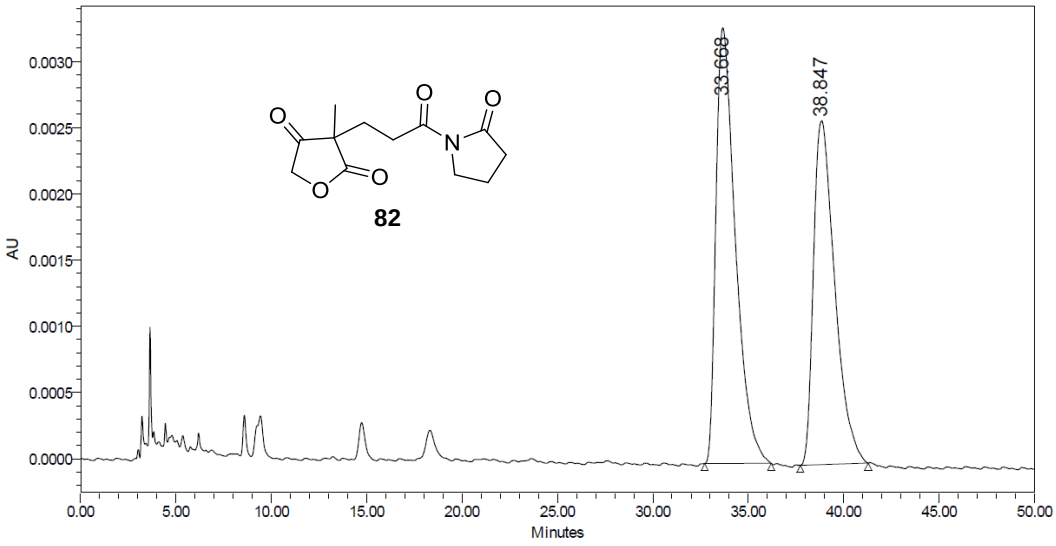

82

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1	33.668	233101	53.66	3291	55.90
2	38.847	201310	46.34	2596	44.10

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Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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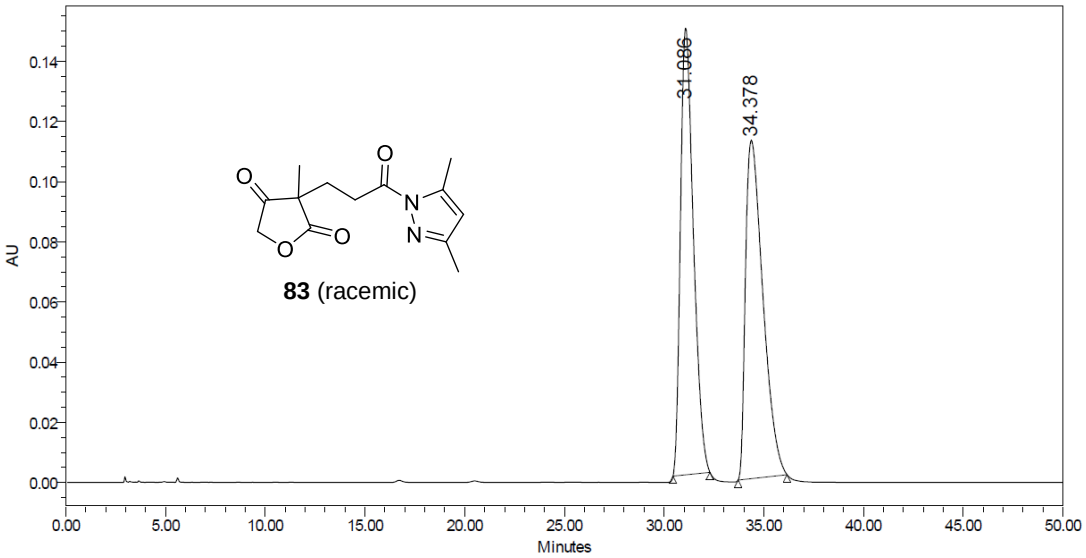

83 (racemic)

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1	31.086	6684308	49.53	148435	56.90
2	34.378	6810704	50.47	112418	43.10

Report Method: Individual Control Report

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Memorial University

Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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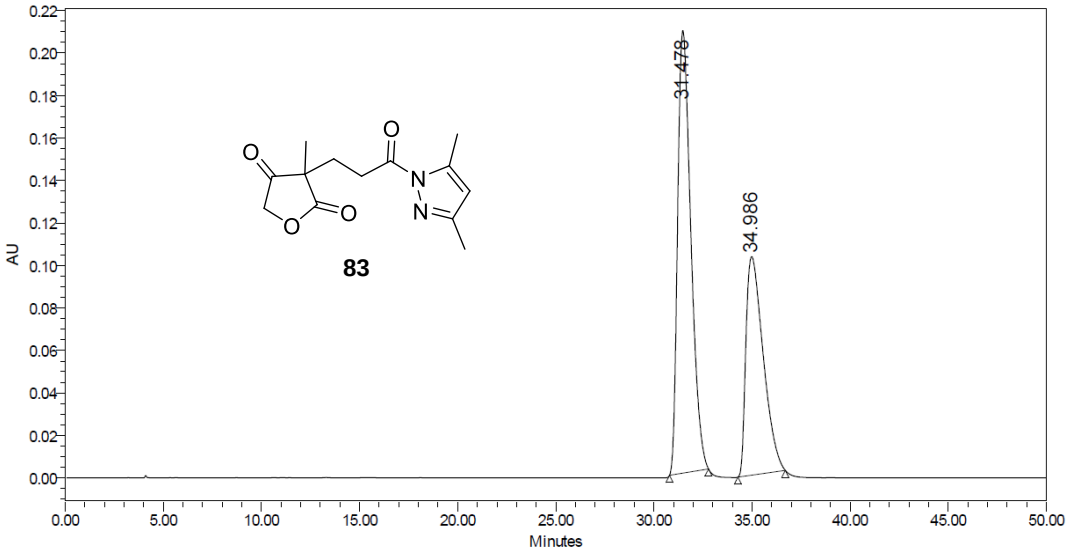

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1	31.478	9745891	60.79	208328	66.95
2	34.986	6286895	39.21	102850	33.05

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Memorial University

Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Run Time:	50.00 Minutes	Channel Desc.:	
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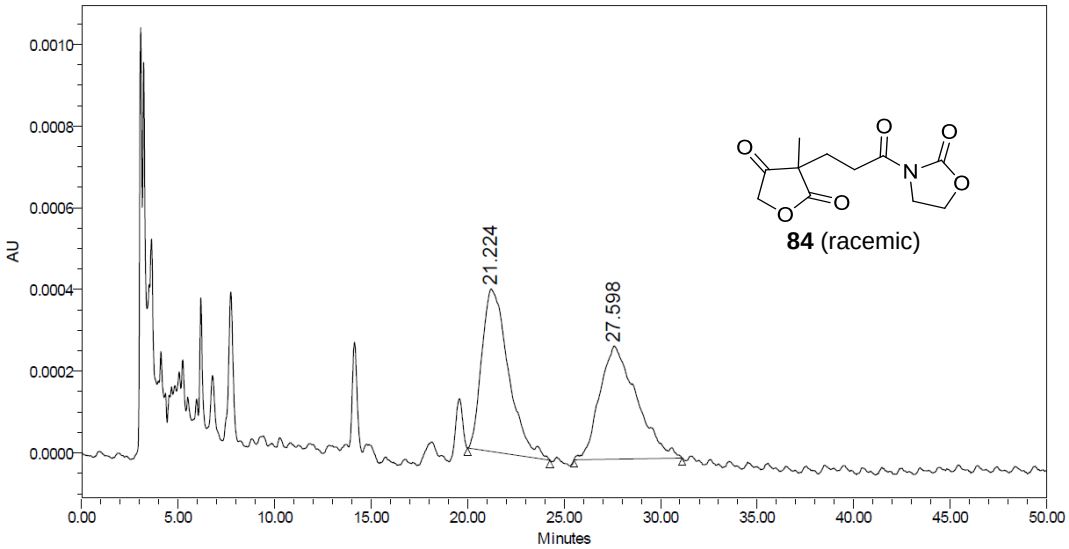

84 (racemic)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.224	38342	50.79	398	58.95
2	27.598	37147	49.21	277	41.05

Memorial University

Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Run Time:	50.00 Minutes	Channel Desc.:	
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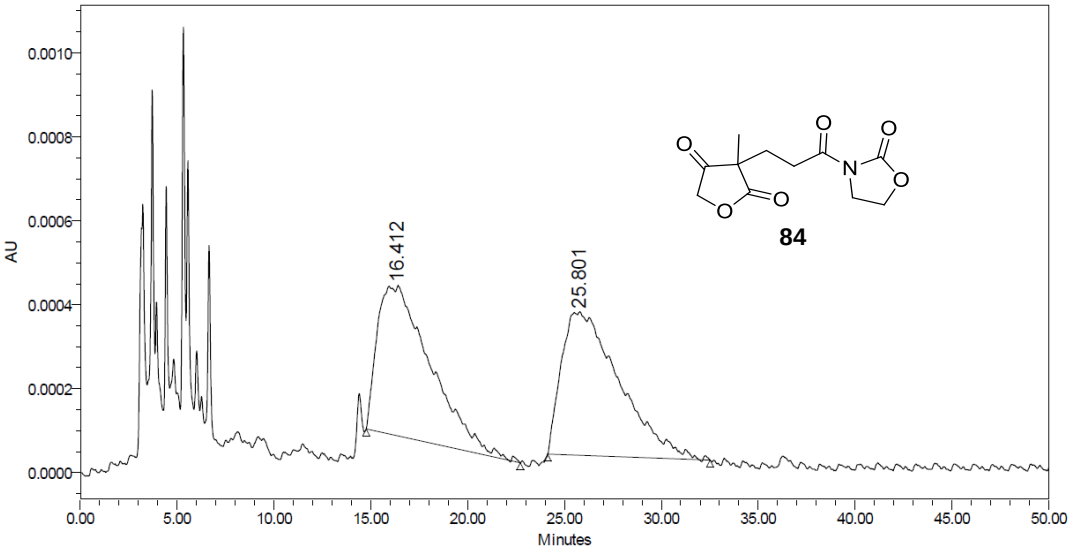

84

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.412	68070	48.88	358	51.17
2	25.801	71176	51.12	342	48.83

Memorial University

Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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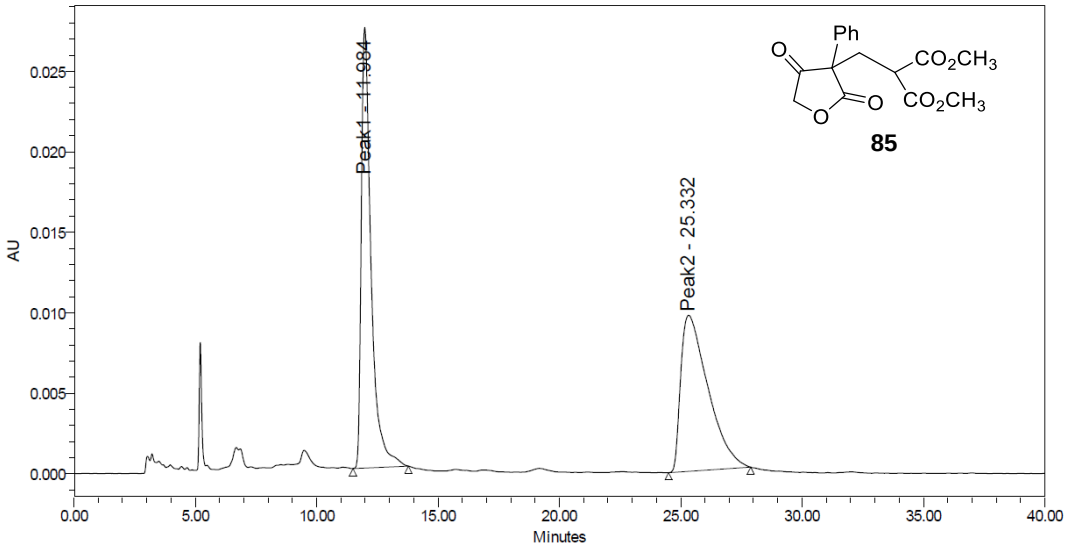
Sample Type:	Unknown	Date Acquired:	22/12/2015 7:31:31 PM NST
Vial:	1	Acq. Method:	AS_H 80%Hex20%IPA2
Injection #:	1	Date Processed:	22/12/2015 8:30:26 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



85

	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	11.984	767116	50.33	27371	73.84
2	Peak2	25.332	756967	49.67	9696	26.16

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Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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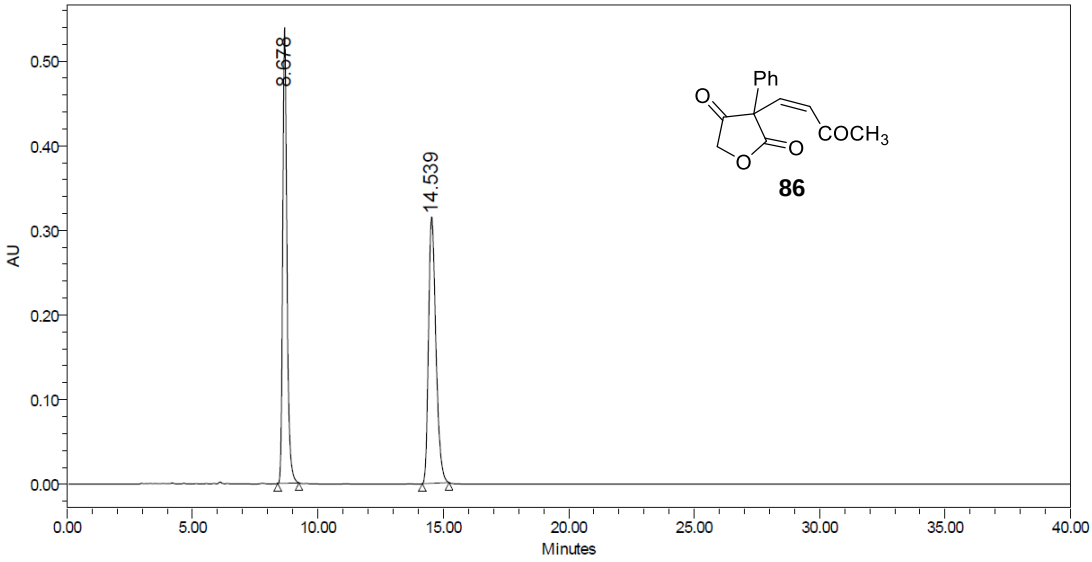
Injection #:	1	Date Processed:	13/01/2017 5:04:01 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



86

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.678	6322306	49.50	539658	63.14
2	14.539	6450754	50.50	314993	36.86

Report Method: Individual Control Report

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Printed: 07/12/2017

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Memorial University

Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Injection #:	1	Date Processed:	25/01/2016 12:28:24 PM NST
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Run Time:	25.00 Minutes	Channel Desc.:	
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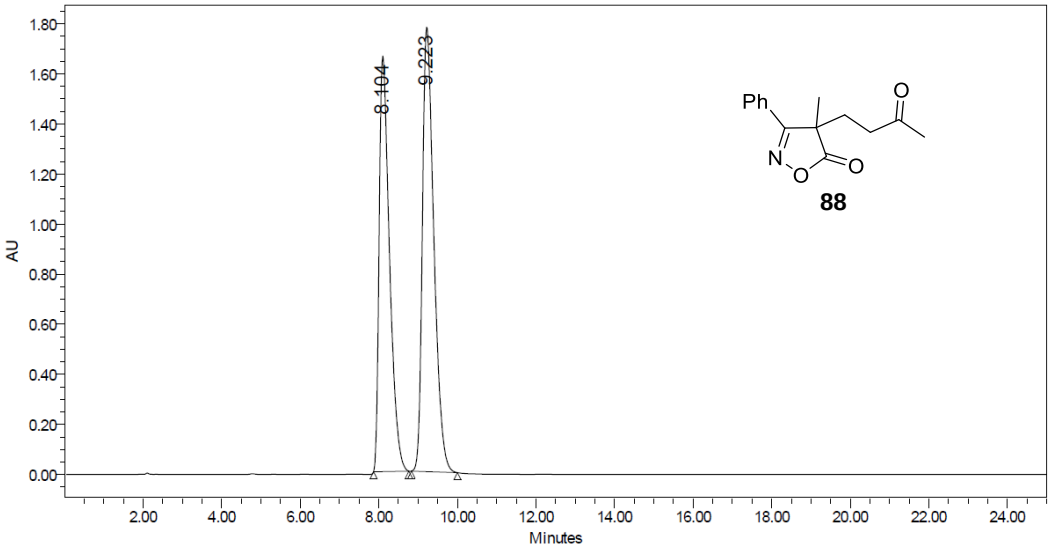


88

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.104	30276624	45.75	1660156	48.29
2	9.223	35906576	54.25	1777472	51.71

Chapter 3

Catalytic Undirected Intermolecular C-H Functionalization of Arenes with 3-Diazofuran-2,4-dione

Synthesis of 3-Aryl Tetronic Acids, Vulpinic Acid, Pinastric Acid, and Methyl Isoxerocomate

A portion of the work described in this chapter has been published in Organic Letters: Manchoju, A.; Pansare, S. V. *Org. Lett.* **2016**, *18*, 5952.

3.1 Introduction

Tetronic acid[1] was first synthesized from ethyl 4-bromoacetoacetate by Wolffe and Schwabe in 1896. Naturally-occurring tetronic acids belong to a large family of compounds that are divided into three categories based on the non-aryl functional group on C6 (Figure 3.1). In 'pulvinic' acids, this group is a $-CO_2H$, whereas in 'vulpinic' acids the group is $-CO_2Me$. A related class of natural products which lack this non-aryl substituent on C6 are called 'pulvinones' (Figure 3.1).[2]

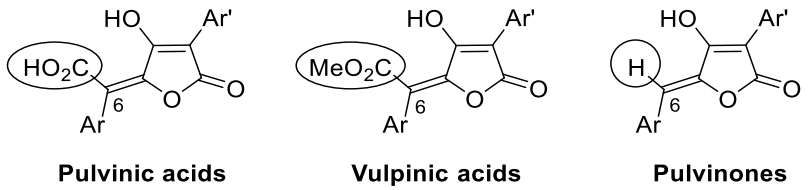


Figure 3.1 Generic structures of naturally occurring tetronic acids.

As a distinctive feature of many natural products, the tetronic acid functionality has attracted considerable attention in recent years.[3] Many tetronic acid derivatives display a wealth of biological activity which include insecticidal and acaricidal,[4] HIV-I protease inhibitory,[5] antineoplastic,[6] antiinflammatory,[7] and cyclooxygenase inhibitory activity.[8] In addition, these tetronic acids are also of interest for their role as pigments in mushrooms and lichens.3 Among a large group of structurally related tetronates that are substituted at C3 with an aryl group are pulvinic acid (**1**, Figure 3.2), vulpinic acid (**2**), 4-hydroxypulvinic acid (**3**), pinastric acid (**4**) and their oxygenated analogues[9] like xerocomic acid (**5**), methylisoxerocomate (**6**) and variegatic acid (**7**). More elaborate congeners include xerocomorubin (**8**),[10a] norbadione A (**9**)[10b] and badione A (**10**).[10b]

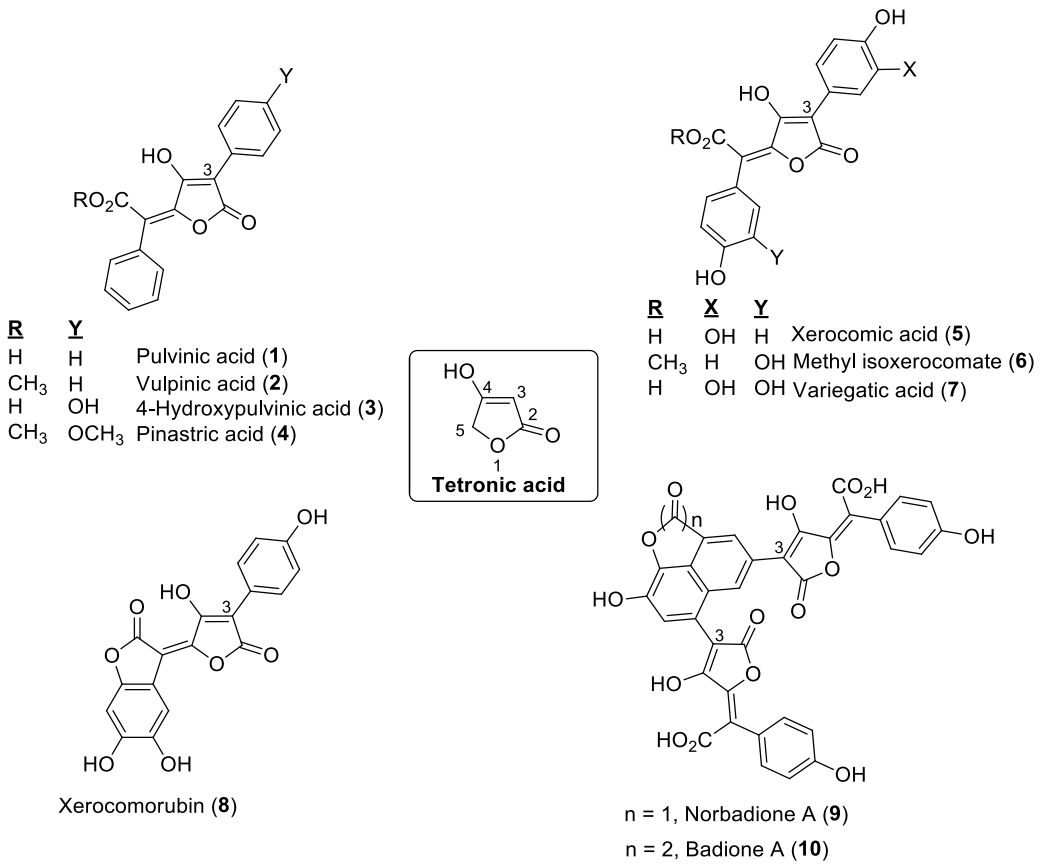
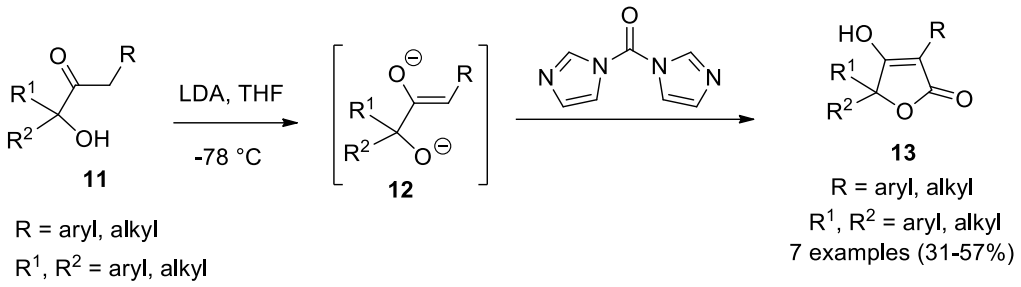


Figure 3.2 Naturally occurring 3-aryl tetronic acid derivatives.

3.2 Known synthetic routes to 3-aryl tetronic acids, vulpinic acids and pulvinic acids

3.2.1 The Smith synthesis of tetronic acids

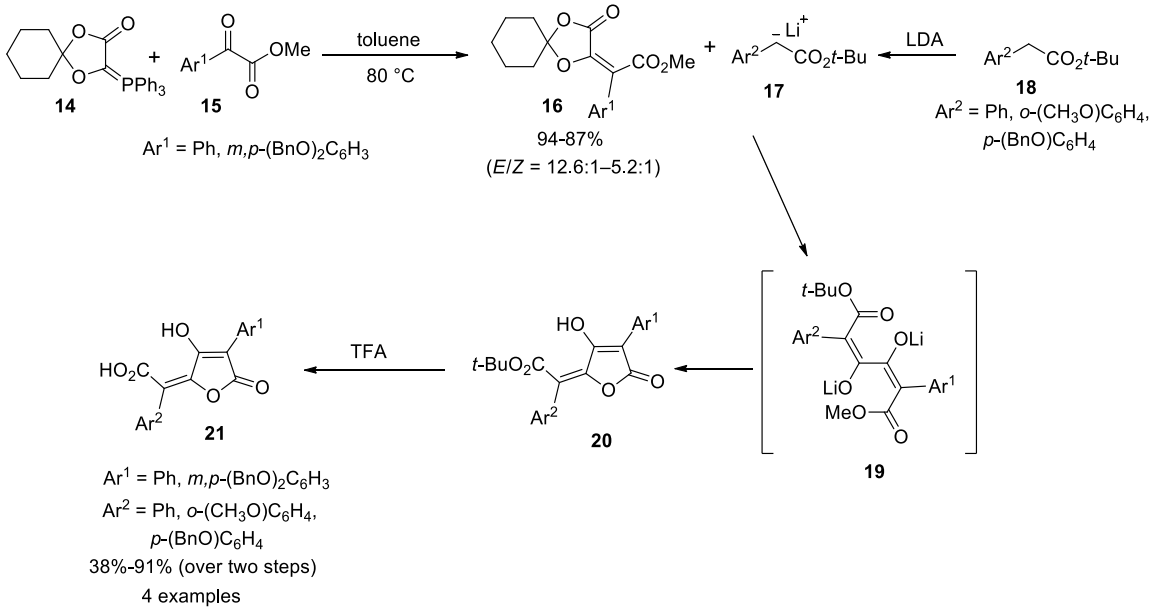
In 1979, Smith and coworkers[11] reported the one-pot syntheses of tetronic acids and pulvinones from α-hydroxyketones **11** (Scheme 3.01). In this methodology, dianions **12**, prepared *in situ* from α-hydroxyketones **11** using LDA, were condensed with 1, 1'-cabonyldiimidazole (CDI) to afford 3-aryl tetronic acids **13**.



Scheme 3.01

3.2.2 The Ramage synthesis of pulvinic acids

In 1984, Ramage and coworkers[12] reported the biomimetic synthesis of pulvinic acids from phosphorane **14** (Scheme 3.02). The reaction of methyl arylglyoxylates **15** with phosphorane **14** gave a mixture of alkenes **16** (*E*-major with trace amount of *Z*) which were separable by column chromatography. Lithium enolates **17**, generated from corresponding *t*-butyl arylacetates **18** using LDA, were treated with *E*-**16** to furnish selectivity *E*-5-arylidenetetronic acids **20**. Hydrolysis of the *t*-butyl ester groups in **20** provided the corresponding pulvinic acids **21**. Distinctly, in this strategy the regioselectivity of cyclization can be controlled by increasing the bulkiness of the alkyl (*t*-butyl) group at the ester functionality.



Scheme 3.02

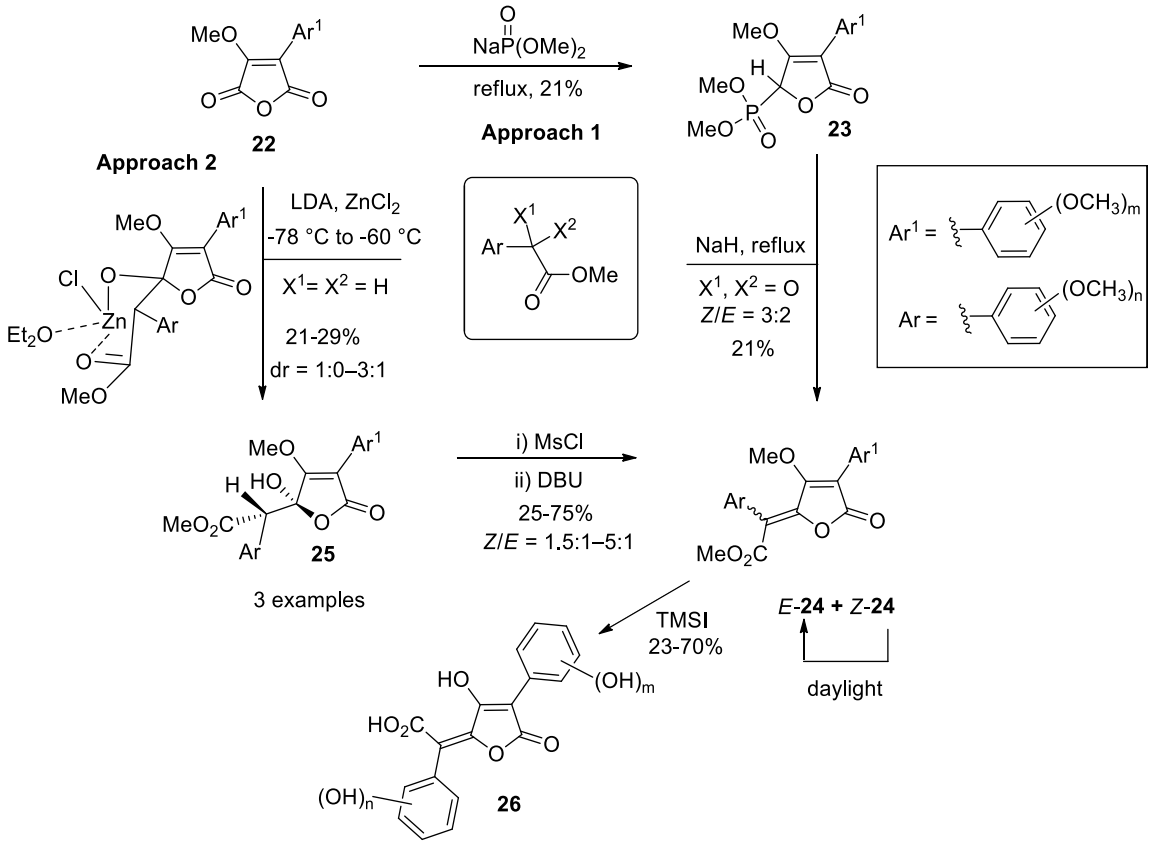
3.2.3 The Pattenden syntheses of pulvinic acids

Pattenden and coworkers[13] reported two methods for the synthesis of pulvinic acids from the corresponding 2-aryl-3-methoxymaleic anhydrides **22** (Scheme 3.03). The first approach involves the conversion of **22** to the phosphonates **23** followed by a Wadsworth-Emmons olefination whereas the second approach relies on Reformatsky-type reactions of **22**.

The reaction between 2-aryl-3-methoxymaleic anhydrides **22** with sodium dimethyl phosphite gave the corresponding phosphonates **23**, which were further treated with arylbenzoyl formates to provide a mixture of *Z* and *E* isomers of *O*-methylvulpinic acids **24**, with the *E*-isomers as major product. The mixture of *Z* and *E* alkenes can be separated by column chromatography or crystallization. In addition, when a solution of *E*/*Z* mixture was exposed to daylight for several days, the Z isomer underwent isomerization to the *E*-

isomers. Treatment of *E*-**24** with trimethylsilyl iodide (TMSI), cleaved the enol *O*-methyl ethers as well as phenolic *O*-methyl ethers to furnish pulvinic acids **26** (Scheme 3.03).

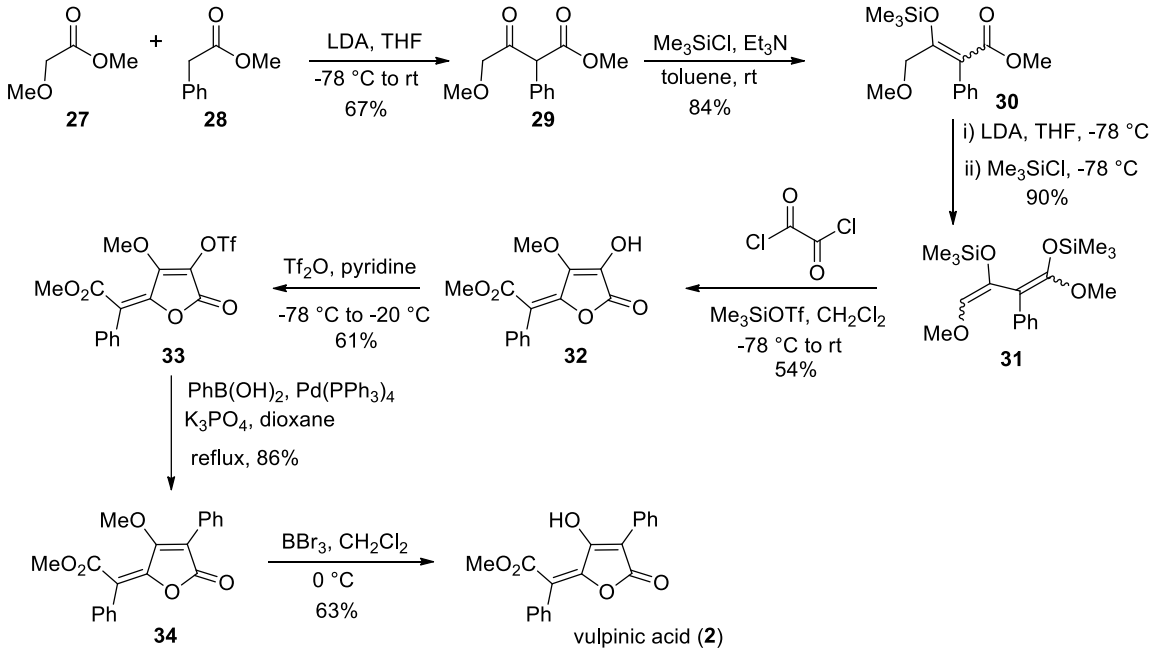
In the second approach (Scheme 3.03), the Reformatsky-type reaction of 2-aryl-3-methoxymaleic anhydrides **22** with zinc enolates derived from the corresponding aryl acetates, prepared by using LDA and $ZnCl_2$, gave hydroxy esters **25**, as single diastereomers in most of the cases. Hydroxy esters **25** were dehydrated by elimination of the corresponding mesylates to provide *Z* and *E* mixtures of the *O*-methylvulpinic acids **25**. As desribed above, photoisomerization and demethylation of **25** provided pulvinic acids **26**.



Scheme 3.03

3.2.4 The Langer synthesis of vulpinic acid (2)

In 2004, Langer and coworkers[14] reported the synthesis of vulpinic acid (**2**, Scheme 3.04). Condensation of **27** with **28** gave ester **29**, which was converted to 1,3-bis-silyl enol ether **31** in two steps *via* silyl enol ether **30**. Compound **31** was treated with oxalyl chloride in the presence of TMSOTf to furnish **32** as a single diastereomer. The *γ*-benzylidenebutenolide **32** was converted to the triflate **33**, which was then subjected to a Suzuki cross-coupling reaction with phenylboronic acid to provide **34**. Demethylation of the enol ether moiety in **34** provided vulpinic acid (**2**).

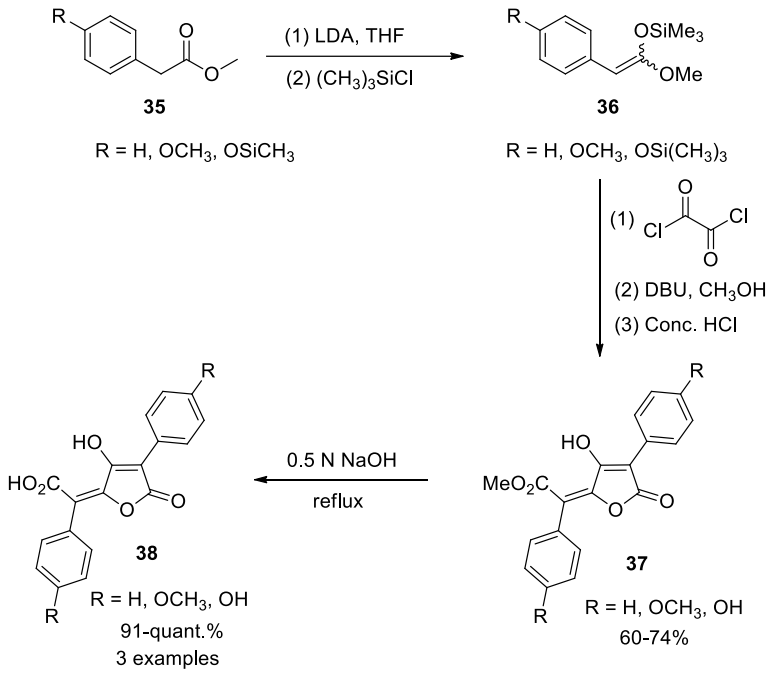


Scheme 3.04

3.2.5 The Le Gall and Mioskowski synthesis of pulvinic acids

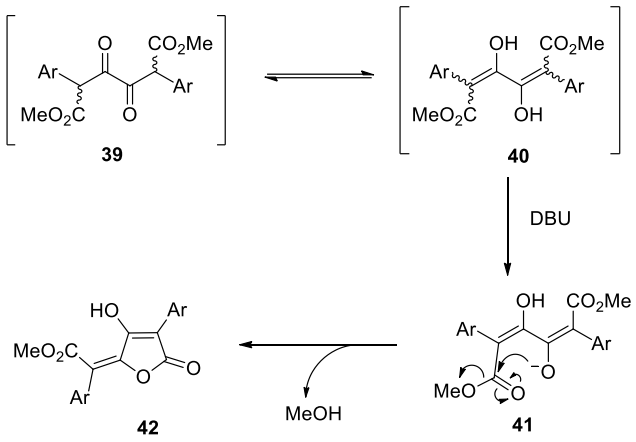
In 2005, the Le Gall and Mioskowski groups[15a] developed the synthesis of symmetrical pulvinic acids **38** from methyl arylacetates **35** (Scheme 3.05). Silyl ketene

acetals **36** were synthesized by treating methyl arylacetates **35** with LDA and trimethylsilyl chloride (TMSCl). Next, reactions were performed between **36** and oxalyl chloride in the presence of DBU, followed by acidification, to provide the corresponding methyl pulvinates **37** (vulpinic acids). These methyl esters **37** were subjected to saponification reactions with aqueous 0.5 N NaOH to furnish corresponding pulvinic acids **38**.



Scheme 3.05

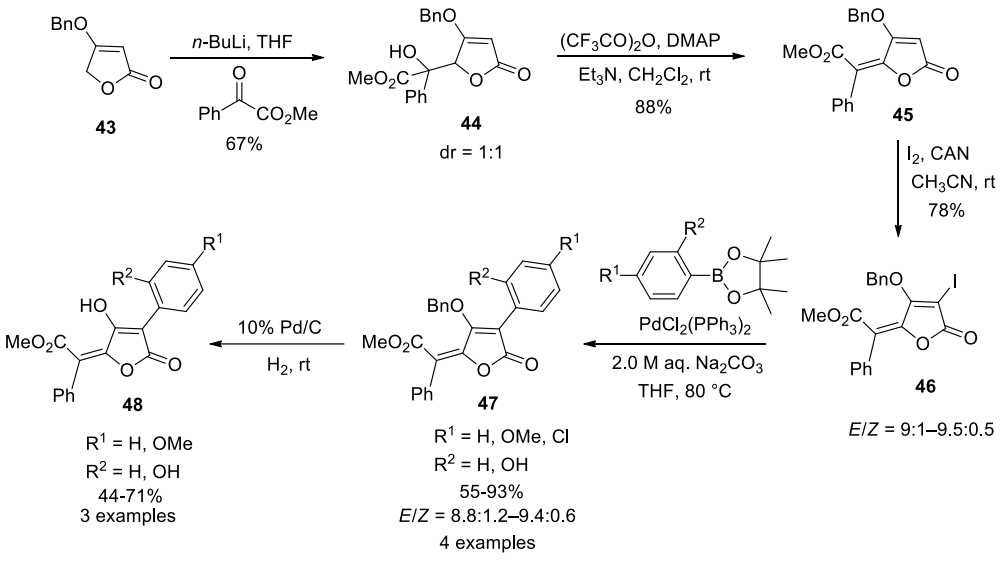
A mechanism has been proposed for the key cyclization reaction, which is the conversion of a diketone **39** to the corresponding vulpinic acid **42** (Scheme 3.06). The diketone **39** can exist in equilibrium with bis-enols **40** in methanol. The treatment of bis-enols **40** with DBU induces a lactonization reaction involving an enolate oxygen and a suitable ester. Acidification provides the vulpinic acid **42** as a single diastereomer (Scheme 3.06).



Scheme 3.06

3.2.6 The Le Gall synthesis of vulpinic acids

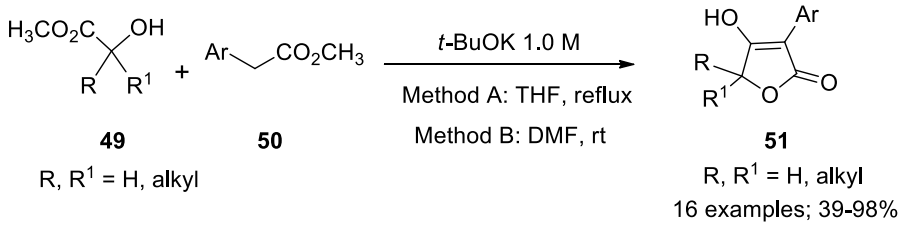
In 2007, Le Gall and coworkers[16] developed a method to synthesize vulpinic acids **48** (Scheme 3.07). Reaction of the anion of **43** and methyl benzoylformate provided the alcohol **44** as a mixture of diastereomers. Subsequent dehydration of **44** in the presence of trifluoroacetic anhydride furnished the *E*-alkene **45** with a small amount of the *Z*-alkene (5-10%). Iodination of **45** with iodine and ceric ammonium nitrate (CAN) provided **46**. Finally, Suzuki-Miyaura cross-coupling reactions of **46** with various aryl boronates provided mixtures of the corresponding alkenes **47**, with the *E*-isomers as the major products. The debenzylation of **47** afforded pure *E*-**48** after removal of the minor *Z*-isomers by column chromatography.



Scheme 3.07

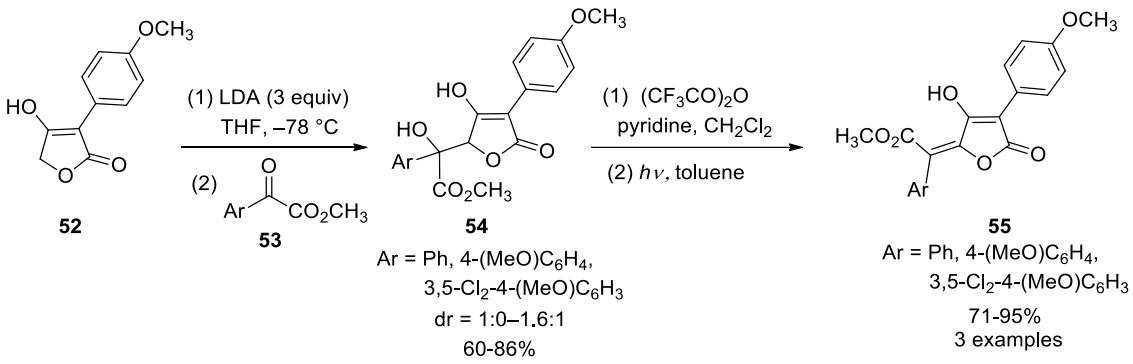
3.2.7 The Le Gall synthesis of tetronic acids

In 2009, Le Gall and coworkers[17] reported the synthesis of 3-aryl tetronic acids from methyl arylacetates **50** *via* transesterification followed by the Dieckmann condensation (Scheme 3.08). The reactions were conducted between methyl arylacetates **50** and methyl hydroxyacetates **49** in the presence of potassium *tert*-butoxide (*t*-BuOK) to provide the corresponding 3-aryl tetronic acids **51** (39-98%). Depending on the substrates, either DMF or THF had to be used as solvents for this reaction.



Scheme 3.08

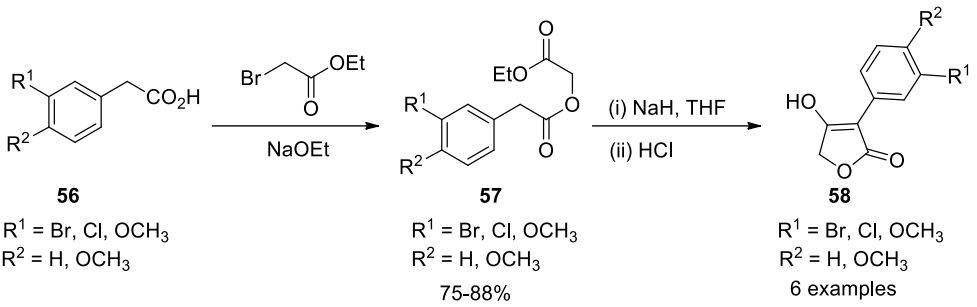
The 3-aryl tetronic acids synthesized in this study were used as starting materials in the synthesis of vulpinic acids (Scheme 3.09). Thus, tetronic acid **52** was treated with lithium diisopropylamide (LDA) to generate the corresponding dianion which was reacted with α-keto esters **53** to give alcohols **54** as a mixture of diastereomers. Dehydration of **54** using trifluoroacetic anhydride and pyridine provided a mixture of *E*-and *Z*- isomers of **55** (*E*/*Z* = 47:53–58:42). These mixtures were subjected to UV irradiation or left exposed to daylight to provide pure *E*-**55**.



Scheme 3.09

3.2.8 The Xiao and Zhu synthesis of 3-aryl tetronic acids from aryl acetic acid

In 2011, the Xiao and Zhu groups[18] reported a synthesis of 3-aryl tetronic acids from the corresponding arylacetic acids **56** as the starting materials (Scheme 3.10). This methodology follows the esterification of arylacetic acids **56** with ethyl bromoacetate to give diesters **57**, which were converted to 3-aryl tetronic acids by the Dieckmann condensation in the presence of NaH, followed by acidification.



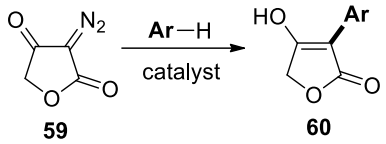
Scheme 3.10

3.3 Objective

As described above, the majority of the reported syntheses of 3-aryl tetronates require a starting material which contains the aryl group that is needed in the target. The majority of these methods use aryl acetic acids (Scheme 3.10),[18] esters (Scheme 3.08)[17] or α-hydroxy alkyl aryl ketones (Scheme 3.01)[11] as the starting materials. An alternative, but synthetically intensive, approach (Scheme 3.04 and 3.07)[14,16] involves the cross-coupling of arylboronic acid derivatives with C3-functionalized tetronic acid derivatives. All of these procedures are primarily limited by the availability of suitably functionalized starting materials and, consequently, methodology that overcomes this limitation, would be useful.

With this objective in mind, a review of the literature indicated a scarcity of reports on the synthetic applications of 3-diazofuran-2,4-dione (**59**, Scheme 3.11),[19] and a sole report describing an undesired, low yield, C-H insertion reaction of this diazo compound.[19c] We were therefore intrigued by the prospect of developing intermolecular aryl C-H insertion reactions of **59**, easily prepared from commercially available tetronic acid by a single step procedure,[19a,c] as a direct route to 3-aryl tetronates (Scheme 3.11). The results of our studies on this strategy and application of the methodology in the synthesis of

vulpinic acid (**2**), pinastric acid (**4**) and methyl isoxerocomate (**6**, Figure 3.2) are presented below.



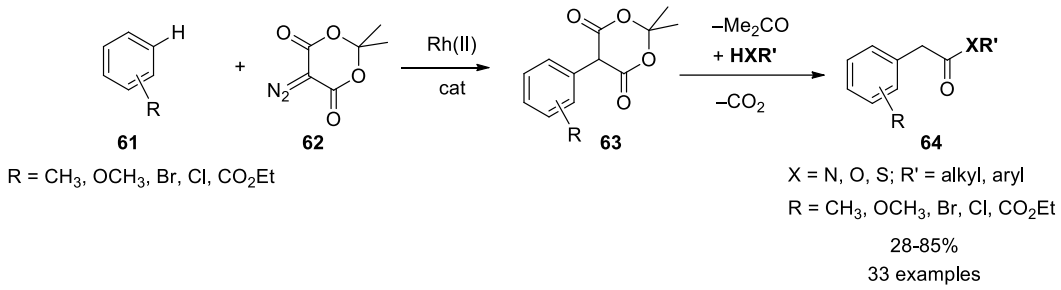
59 **60**

Scheme 3.11 A strategy for the synthesis of 3-aryl tetronic acids

3.3.1 Previous studies on C-H insertion reactions of arenes and diazo 1,3-dicarbonyl compounds

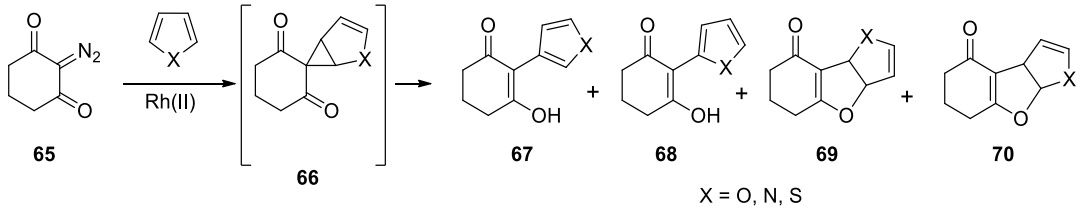
Intramolecular and substrate-directed C-H functionalization of arenes with diazo compounds are well-known.[20] Undirected, intermolecular, arene C-H functionalization reactions[21a] have also been investigated. The majority of these studies have examined *a*-aryl diazo esters[21b-i] or diazooxindoles[21j-l] and only a few studies are reported for diazo 1,3-dicarbonyl compounds.[21m-p] The C-H insertion reactions of diazo 1,3-dicarbonyl compounds are summarized below (Schemes 3.12-3.15).

Recently, Best and coworkers reported[21m] a one-pot synthesis of arylacetic acid esters, thioesters and amides **64** using C-H insertion of Meldrum's acid-derived diazo compound **62** with electron rich-arenes **61** (Scheme 3.12). This methodology employs C-H insertion reactions of **62** with arenes **61** to give **63**, which were further condensed with alcohols or thiols or amines, followed by decarboxylation in the presence of trimethylamine, to afford **64**.



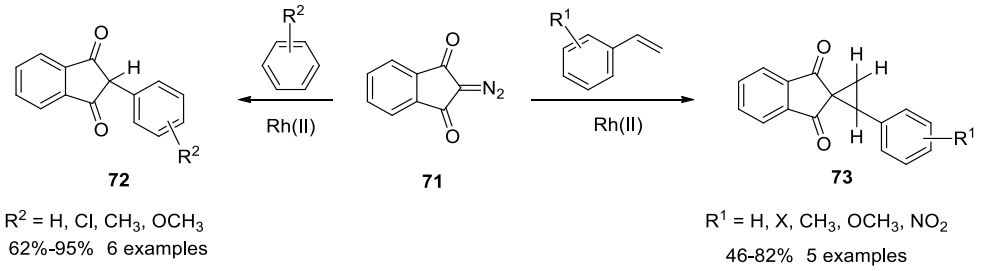
Scheme 3.12

Pirrung and coworkers[21n] studied rhodium (II)-catalyzed reactions of a cyclic diazo compound, namely 2-diazo-1,3-cyclohexanedione (**65**), with heteroaromatics (Scheme 3.13). These reactions provide a mixture of C-H insertion products as regioisomers **67**, **68** and 1,3 dipolar cycloaddition products **69** and **70**.



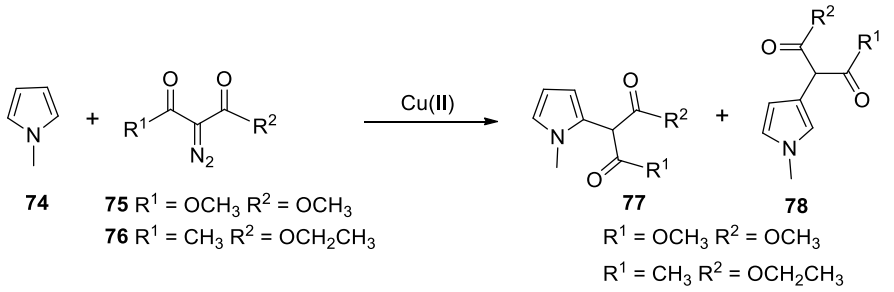
Scheme 3.13

In related studies, Shechter and coworkers[22o] examined the reactions of arenes, and olefins with 2-diazo-l,3-indanedione (**71**) in the presence of $Rh_2(OAc)_4$ as the catalyst (Scheme 3.14). The reactions of **71** with arenes provide the corresponding C-H insertion products **72**. On the other hand, reactions of **71** with olefins afford spirocyclopropanes **73**.



Scheme 3.14

Maryanoff reported[22p] that copper (II) catalyzed reactions of dimethyl diazomalonate (**75**) and ethyl 2-diazoacetoacetate (**76**) with *N*-methylpyrrole (**74**) provide the corresponding C-H insertion products as regioisomers **77** and **78** (Scheme 3.15).

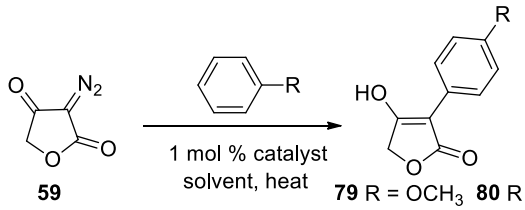


Scheme 3.15

3.4 Results and Discussion

As described above (Scheme 3.12-3.15), only four studies addressed the C-H insertion reactions of diazo 1,3-dicarbonyl compounds and arenes. Given the relative shortage of information available on the key step of our proposed synthetic plan, a survey of catalysts and reaction conditions was necessary. Accordingly, we first attempted the reaction of **59** with anisole in the presence of $Cu(OTf)_2$,[21l] $Co(OAc)_2$ [22] and $(Ph_3P)AuCl/AgSbF_6$[21d] as catalysts. With $Cu(OTf)_2$, **79** was obtained in low yield (11%, Table 3.1, entry 1). Although the Co- and Au-derived catalysts are known to promote diazo decomposition, only unreacted **59** was observed in these reactions.

Table 3.1 Optimization of the intermolecular aryl C−H insertion reaction of **59**



59 **79** R = OCH_3 **80** R = Ph

Entry[a]	Catalyst	Solvent	*t* (h)	Product	Yield (%)[b]
1	$Cu(OTf)_2$	-	26	**79**	11 (36)[c]
2	$Co(OAc)_2$	-	10	-	-
3	$(PPh_3)AuCl/AgSbF_6$	-	76	-	-
4	$Rh_2(OAc)_4$	-	6	**79**	96
5	$Rh_2(OAc)_4$	$(CH_2)_2Cl_2$[d]	12	**80**	36
6		CH_2Cl_2[d]	79		21 (34)[c]
7		$PhCF_3$[e]	168		47 (55)[c]
8		[bmim]PF_6[d]	65		13
9		[bmim]BF_4[d]	96		16 (22)[c]
10	$Rh_2(CF_3CO_2)_4$	$(CH_2)_2Cl_2$	24		27
11		CH_2Cl_2	96		-
12		$PhCF_3$[e]	5		51 (67)[f]
13		$PhCF_3$[e]	21		35(46)[f,g]
14		[bmim]PF_6	92		19 (22)[c]
15		[bmim]BF_4	72		42
16	$Rh_2(NHCOC_3F_7)_4$	$(CH_2)_2Cl_2$	5		19
17		CH_2Cl_2	7		-
18		$PhCF_3$[h]	2.5		23
19		[bmim]PF_6	22		21
20		[bmim]BF_4	55		23

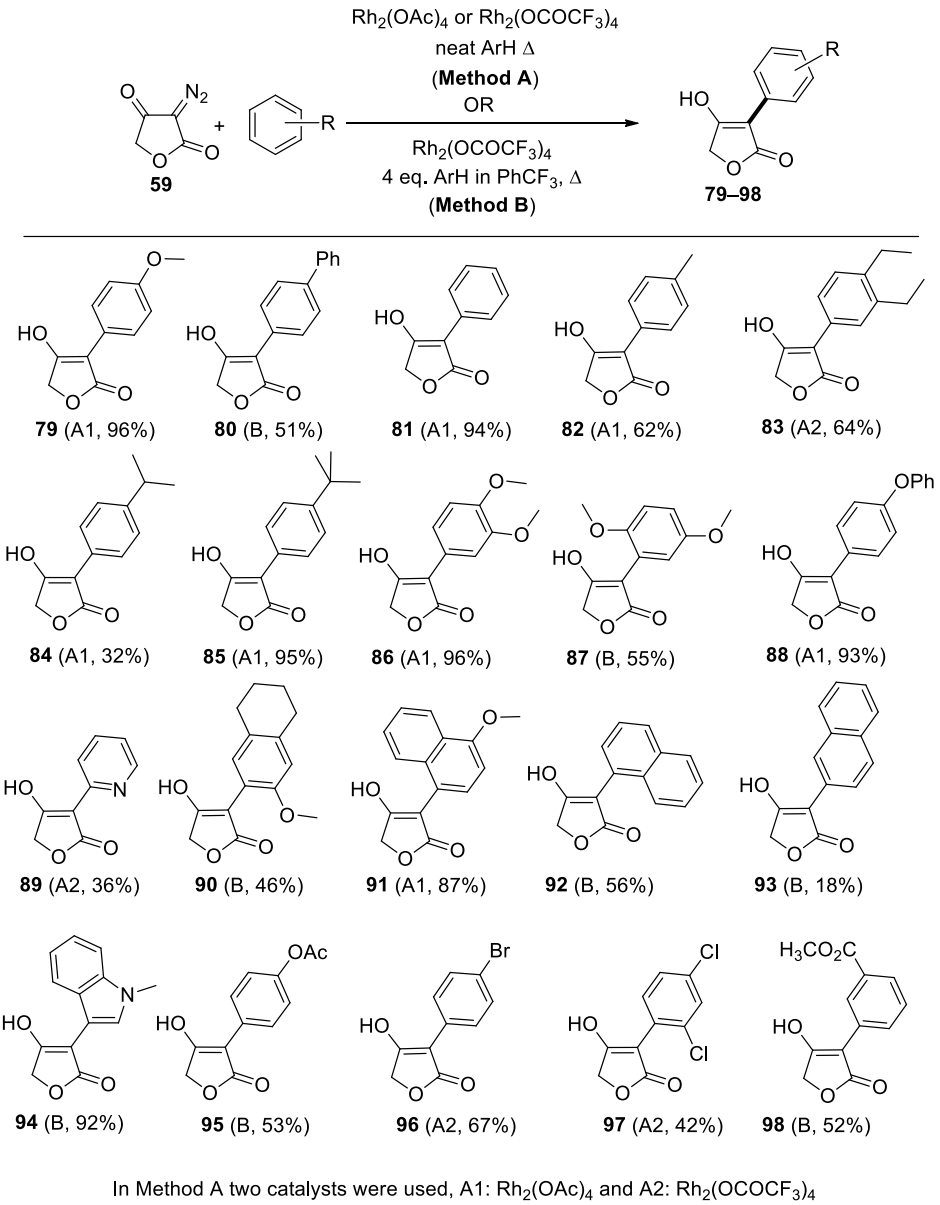
[a]anisole (entries 1-4) and biphenyl (entries 5-20) as arenes. [b]isolated yields. [c]based on recovered **59**. [d]at reflux or at 100 °C for ionic liquids. [e]at 70 °C. [e]at 100 °C. [f]including regioisomer. [g]reaction with 2 equivalents of biphenyl. [h]reaction at 80 °C.

We therefore turned to the more conventional rhodium-based catalysts. Interestingly, heating a solution of **59** in anisole in the presence of $Rh_2(OAc)_4$ provided **79** in excellent yield (96%) as a single regioisomer (Table 3.1, entry 4). This procedure (Method A) was suitable for simple arenes which could be used as the solvent and then easily separated from the tetronic acid product and recovered.

In order to expand the scope of the methodology to other arenes, an optimization of the insertion reaction was conducted by varying the solvent, the catalyst and the stoichiometry of the arene. These studies, with biphenyl as the representative arene, are summarized in Table 3.1.

Conventional chlorinated solvents, ionic liquids and α, α, α-trifluoromethylbenzene were selected as the reaction media and a set of rhodium (II) catalysts differing in the ligand were screened. The choice of rhodium catalysts that are more electrophilic than $Rh_2(OAc)_4$ was based on previous studies on competitive intramolecular reactions of diazo carbonyl compounds [23] in which electron-deficient rhodium catalysts favoured aromatic substitution (net C-H insertion) reactions over competing cyclopropanation. As seen from Table 3.1, almost all of the reactions provided **80**, but α, α, α-trifluoromethyl benzene was clearly a superior solvent (Table 3.1, entries 7 and 12), and $Rh_2(CF_3CO_2)_4$ is the catalyst of choice (compare entries 7, 12 and 18 in Table 3.1). The best results were obtained with an excess of biphenyl (4 equiv, Table 3.1, entry 12) and reducing this amount was not beneficial (46% yield with 2 equiv. of biphenyl; Table 3.1, entry 13). This procedure ($PhCF_3$ as the solvent, $Rh_2(CF_3CO_2)_4$ as the catalyst

and 4 equiv of the arene; Method B) or Method A, described above, were applicable to the C-H insertion reactions of **59** with a variety of arenes to provide **79**-**98** (Figure 3.3).



In Method A two catalysts were used, A1: $Rh_2(OAc)_4$ and A2: $Rh_2(OCOCF_3)_4$

Figure 3.3 Intermolecular aryl C-H insertion of **59**

The C-H insertion reactions of **59** with alkyl benzenes and with electronically activated arenes proceeded readily and in moderate to good yields (Method A, 12 examples,

72% average yield; Method B, 7 examples, 60% average yield). Interestingly, **59** also reacted with methyl benzoate to provide **98** (52%), but reactions with more electron-deficient arenes such as nitrobenzene, acetophenone and benzonitrile were unsuccessful. The regiochemistry of C-H functionalization is what would be expected for electrophilic aromatic substitution of the arene[24] except for the C-H insertion reaction of pyridine. Although the reason for this observation is not known at this time, it is plausible that the nitrogen in the pyridine ring directs the C-H insertion to proceed at C2 instead of C3. In a few cases, regioisomeric products (**80**, *p*/*o* = 3.1:1; **92**/**93** = 3.1:1; **96**, *p*/*o* = 3.5:1), which were easily separated, were obtained. The results suggest that the carbenoid derived from **59** reacts with the arenes as an electrophile. This reactivity is consistent with the superior performance of $Rh_2(CF_3COO)_4$ which presumably increases the electrophilicity of the bound carbene.[23]

Based on these observations, we propose a plausible mechanism for the C-H insertion reaction (Figure 3.4). Addition of the carbanion **59** to the rhodium metal followed by elimination of N_2 provides an electrophilic carbenoid **99** (acceptor/acceptor substituted carbenoid). Addition of the nucleophile, such as an alkoxy benzene, to the electrophilic carbenoid carbon in **99** followed by elimination of the rhodium catalyst generates the intermediate **101**. Transfer of a proton to the tetronate oxygen, with concomitant aromatization of **101**, provides **102** which is the product of a 'net insertion' of tetronic acid into the arene C-H bond.

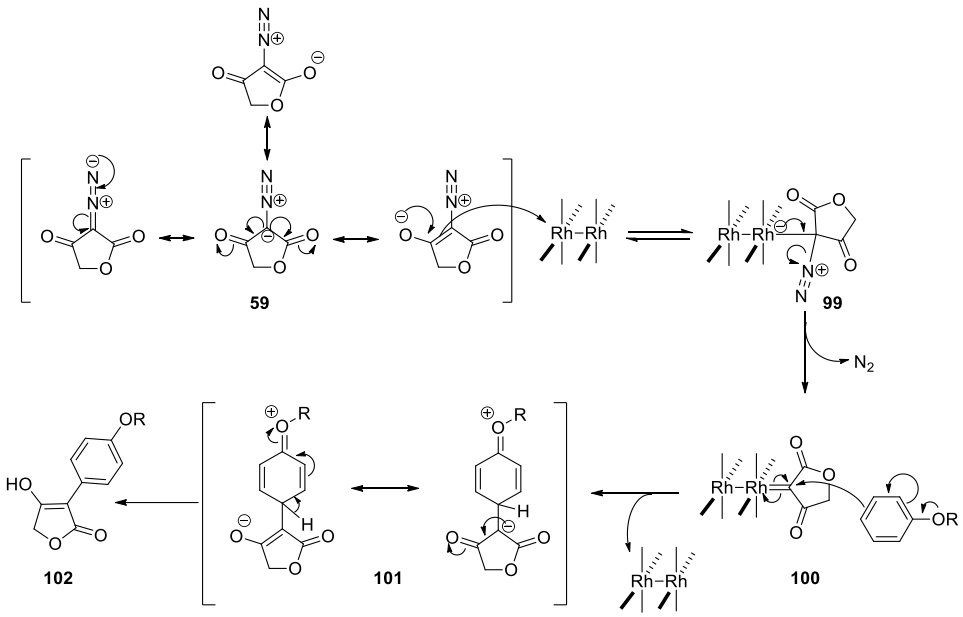


Figure 3.4 A plausible mechanism for the C-H insertion reactions

3.4.1 Synthesis of naturally-occurring tetronic acid derivatives

Having established a general procedure for preparing 3-aryl tetronic acid derivatives, we next examined the application of our method in the synthesis of selected, naturally-occurring pulvinic acids (Figure 3.2). While the conversion of 3-aryl tetronic acids to pulvinates is well-known (Schemes 3.2 3.3 and 3.4),[12,13a,14] an objective of the present study was to develop a modular functionalization of **59** by first introducing the arylidene functionality at C5 (Figure 3.5) and then adding the C3 aryl group employing the C-H insertion procedure. Compared to current methods for pulvinic acid synthesis, our procedure would use **59** as the common starting material for all of the structurally related tetronate natural products. This strategy is summarized in Figure 3.5.

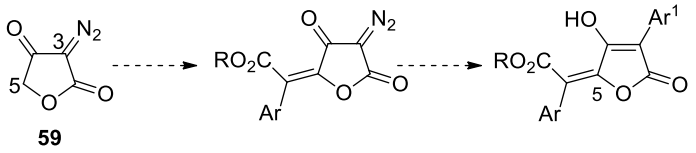


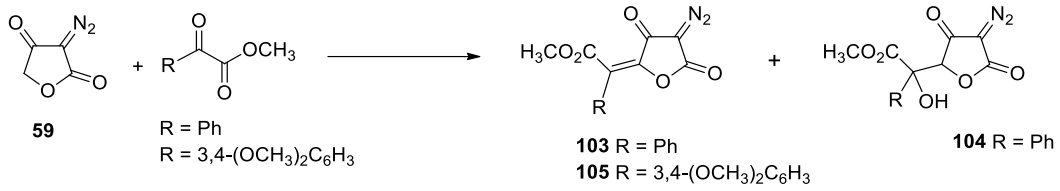
Figure 3.5 Strategy for the synthesis of naturally occurring pulvinates from **59**.

As described in section 3.2, previous syntheses of C5-arylidene tetronic acid derivatives from 3-aryl tetronic acids have relied on protocols that involve multi-step assembly of the tetronate ring (schemes 3.01, 3.03 and 3.04),[11,13b,14] or Wittig reaction of a preformed C3-substituted tetronate derivative (scheme 3.03).[13,12] More recent strategies also involve several steps, specifically: (a) an aldol reaction of a C3-substituted tetronic acid derivative with an α-keto ester; (b) dehydration of the aldol product by mesylation and elimination,[12] or by conversion first to the trifluoroacetate followed by elimination, and (c) photoisomerization of the mixture of isomeric alkenes so obtained to the naturally-occurring *E*-isomer (Schemes 3.03 and 3.09).[13,17] Stereoisomers of the required alkene products are also obtained in the earlier procedures.[12,14,18b] Clearly, an alternative to these multi-step procedures, and especially to the stereorandom synthesis of the arylidene portion at C5, would be useful.

Our search for alternative procedures focused on the possibility of using a mild aldolization protocol that would not affect the diazo group in **59**. Initial attempts with **59** and the methyl benzoylformate in the presence of LDA (Table 3.2, entry 1) or $MgBr_2$ and triethylamine[25a] (Table 3.2, entry 2) provided a very low yield of the required aldol product. However, the use of a stronger Lewis acid (Table 3.2, entries 3 and 4)[25b] provided a mixture of the aldol product **104** and the dehydration product **103**. A brief optimization revealed

that warming the reaction mixture (0 °C) provided only **103** (64%, Table 3.2, entry 5) with excellent diastereoselectivity (*E*/*Z* = ~40:1).[26] These optimized reaction conditions were used for aldol condensation reactions in subsequent studies.

Table 3.2 Optimization of aldol condensation reaction of **59**.



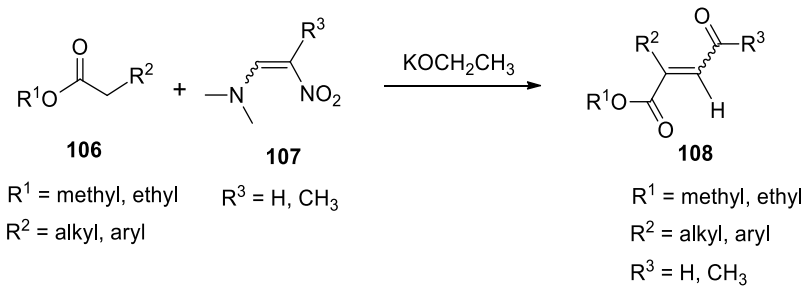
S. No.	Reagents and conditions	Product	Yield[a]	104[a]
1	LDA, THF, -78 °C, 1.5 h to 0 °C, 1 h	**103**	-	6
2	$MgCl_2$, Et_3N, TMSCl, EtOAc, rt, 96 h		-	<5
3[b]	$TiCl_4$, -78 °C to 0 °C, 1.5 h Et_3N, -78 °C, 1.5 h		20	67
4[c]	$TiCl_4$, -78 °C, 30 min Et_3N, -78 °C, 40 min		61	28
5[c]	$TiCl_4$, -78 °C, 30 min Et_3N, -78 °C, 3.5 h to 0 °C, 6 h		64	-
6[d]	$TiCl_4$, -78 °C, 30 min Et_3N, -78 °C, 1 h		-	-
7	$TiCl_4$, -78 °C, 30 min Et_3N, -78 °C, 4 h		33	25
8	$TiCl_4$, -78 °C, 30 min Et_3N, -78 °C, 30 min to 0 °C, 5 h		61	-
9	$TiCl_4$, -78 °C, 30 min Et_3N, -78 °C, 40 min	**105**	60	

[a]isolated yields. [b]reaction with 1.5 equiv of $TiCl_4$ and 2 equiv of Et_3N. [c]reaction with 3 equiv of $TiCl_4$ and 3 equiv of Et_3N. [d]reaction with 7 equiv of $TiCl_4$ and 7 equiv of Et_3N.

Similarly, **105** was also obtained as a single isomer (60%, Table 3.2, entry 9) using this procedure but with methyl 3,4-dimethoxybenzoylformate.

3.4.2 Determination of stereochemistry of aldol condensation products

The geometry of the aldol condensation products, **103** and **105** has been assigned by comparison of characteristic chemical shifts of *E* and *Z* isomers of structurally similar compounds reported in the literature. Lerche[27b] reported the reactions of esters **106** with nitroenamines **107** in the presence of a base to give mixtures of *E*- and *Z*- alkyl-4-oxo-2-arylpentenoates **108** (Scheme 3.16).



Scheme 3.16

The ^{1}H NMR chemical shifts of selected hydrogen atoms in **109**, obtained by the above methodology, were utilized to assign the stereochemistry of **103** obtained in our studies. The ^{1}H NMR signal for the ester methyl group (CO_2CH_3) in *Z*-**109** appears at δ 3.97, whereas in *E*-**109**, it appears at δ 3.86 (Figure 3.6). Notably, the ester methyl group in *Z*-**109** (δ 3.97) experiences a downfield shift due to anisotropic deshielding by the neighboring carbonyl group (CH_3CO) group, as compared with the ester methyl group in *E*-**109** (δ 3.86, Figure 3.6).

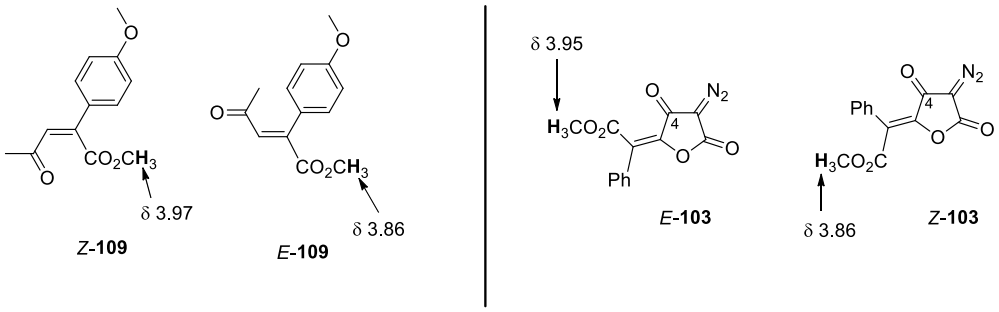
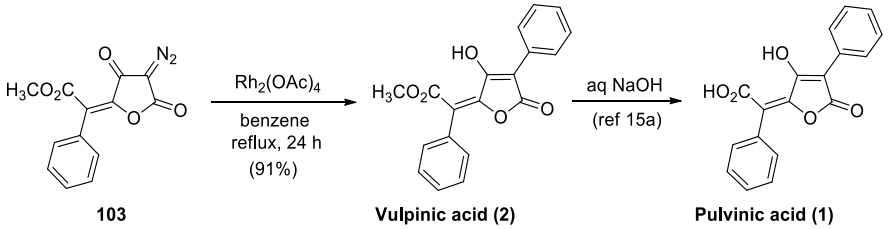


Figure 3.6

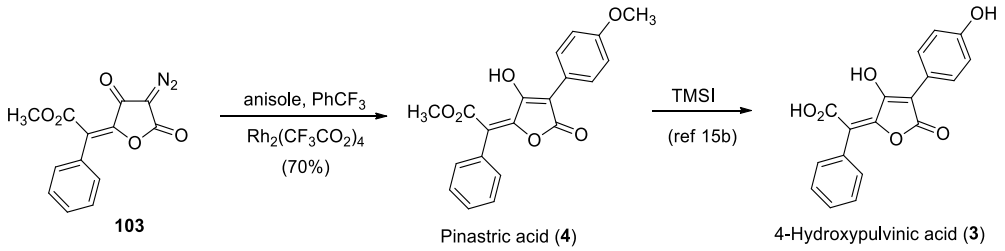
In our studies, a similar trend in chemical shift for the methyl ester in **103** has been observed. In *E*-**103**, the ester methyl group appears downfield, at δ 3.95, compared to the *Z*-**103** isomer, in which the ester methyl group is at δ 3.86. This is due to the anisotropic deshielding by the C4 carbonyl group in *E*-**103**. The geometry of **105** is assigned by anology to **103**.

With **103** and **105** in hand, their C-H insertion reactions were examined. Gratifyingly, Rh(II)-catalyzed reactions of **103** in benzene provided vulpinic acid (**2**, 91%, Scheme 3.17). The transformation of **2** to pulvinic acid (**1**) has been reported[15a] by Le Gall.



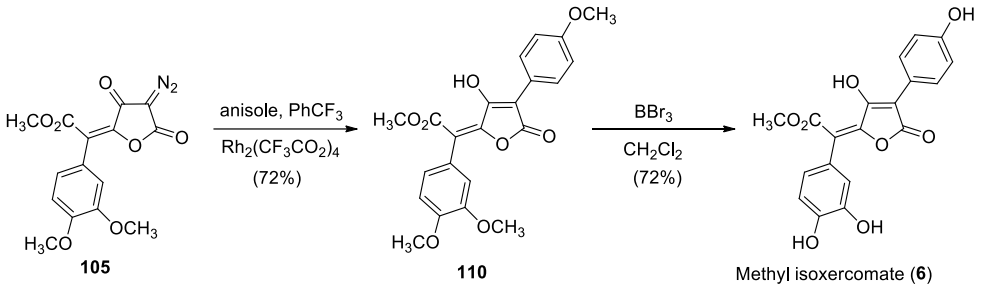
Scheme 3.17 Synthesis of vulpinic acid (**2**)

Similarly, the C-H insertion reaction of **103** with anisole (4 equiv in $PhCF_3$, Method B) in the presence of $Rh_2(CF_3COO)_4$ furnished pinastric acid (**4**, 70%, Scheme 3.18). The conversion of **4** to 4-hydroxypulvinic acid (**3**) has been reported[15b] by Pattenden.



Scheme 3.18 synthesis of pinastric acid (**4**)

Next, the synthesis of methyl isoxerocomate (**6**) was studied. The C-H insertion reaction of **105** with anisole provided **110** (72%). Chemoselective demethylation of the aryl methyl ethers in **110** with BBr_3 furnished methyl isoxerocomate (**6**, 72%, Scheme 3.19).

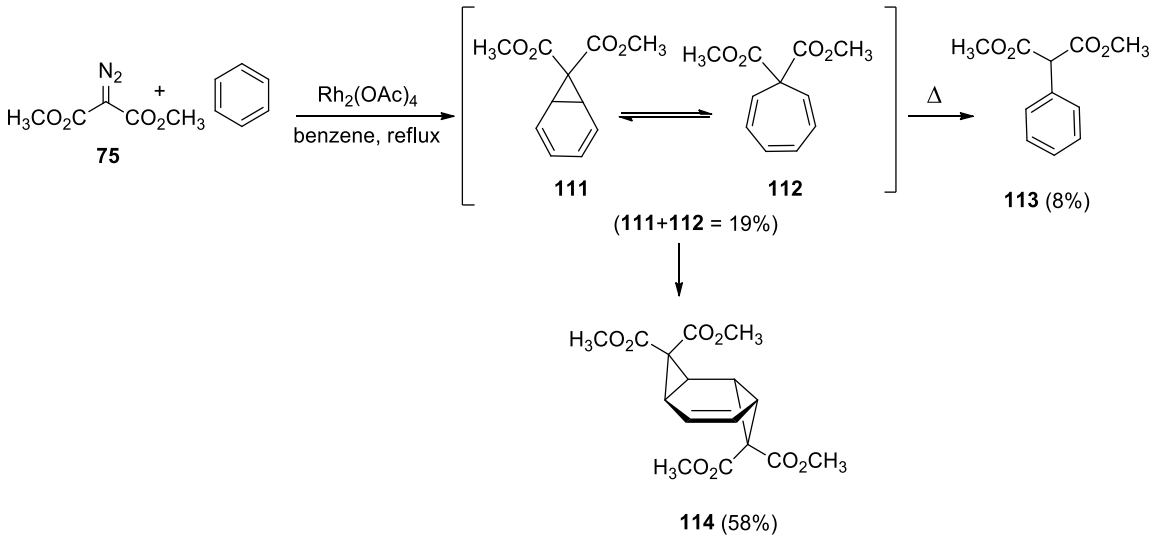


Scheme 3.19 Synthesis methyl isoxerocomate (**6**)

The formation of **2**, **4**, and **6** also confirms the stereochemical assignments for **103** and **105** which were initially based by analogy to structurally-related compounds (Section 3.5.1.1).

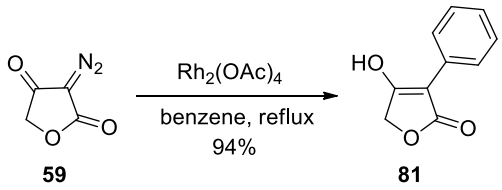
3.4.3 The unique reactivity of diazotetronic acid (59)

It is well known that stabilized diazo compounds such as diazomalonate react with an aromatic ring in a manner that is distinct from the C-H insertion reactions of diazotetronic acid **59**. This, more conventional, reaction is the Büchner ring expansion reaction between aromatic compounds and carbenes to generate norcaradiene which can exist in equilibrium with cycloheptatriene (Scheme 3.20). From previous reports,[27] Rh(II)-catalyzed reactions of dimethyl diazomalonate and methyl diazoacetate with arenes provided the corresponding norcaradiene and bis-cyclopropanation products with only trace amounts of C-H insertion products. For example,[27] the reaction of dimethyl diazomalonate **75** with benzene at the reflux temperature in the presence of $Rh_2(OAc)_4$ provided a mixture of **111**, **112**, **113** and **114** (Scheme 3.20). A portion of the equilibrium mixture of **111** and **112** is converted into the bis-cyclopropanation product **114** by cyclopropanation of **111** during the reaction.



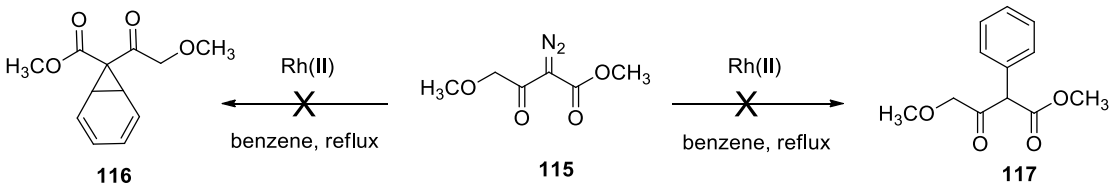
Scheme 3.20

In contrast, the reaction of diazotetronic acid (**59**) in benzene in the presence of $Rh_2(OAc)_4$ at reflux provided the insertion product **81** in 94% yield. Interestingly, this reaction afforded only insertion product **81** without any Büchner ring expansion products.



Scheme 3.14

Interestingly when diazo compound **115**, an open-chain analogue of **59**, was employed in reactions with benzene in the presence of $Rh_2(OAc)_4$ or $Rh_2(CF_3COO)_4$, both reactions generated complex mixtures which contained neither the insertion product **117** or any cyclopropanation products **116** (Scheme 3.21). These observations suggest that diazotetronic acid (**59**) has unusual reactivity that favors C-H insertion reactions with arenes in the presence of Rh(II) catalysts.



Scheme 3.21

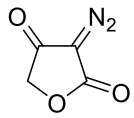
3.5 Conclusion

In conclusion, a one-step synthesis of 3-aryl tetronic acids has been developed from 3-diazofuran-2,4-dione (**59**). The synthesis of vulpinic acid (**2**), pinastric acid (**4**) and methylisoxercomate (**6**), as well as a formal synthesis of pulvinic acid (**1**) and 4-hydroxypulvinic acid (**3**) was achieved in three steps from commercially available tetronic acid. To the best of our knowledge, the two-step functionalization of **59** offers the shortest route to these natural products. The methodology provides direct access to a wide range of 3-aryl tetronates and has the advantage of furnishing stereoisomerically-pure 5-arylidene tetronates. We anticipate that our modular strategy will be useful for preparing natural product-like libraries of tetronic acid derivatives by systematic variation of the C3 aryl group and the aryl group in the α-keto ester used in the aldol condensation.

3.6 Experimental Section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 were distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system.

3-Diazofuran-2,4(3*H*,5*H*)-dione (59):[19c]



To a solution of tetronic acid (1.50 g, 15.0 mmol) in acetonitrile (20 mL) were added tosyl azide (2.90 g, 15.0 mmol) followed by dropwise addition of triethylamine (2.09 mL, 15.0 mmol) over 10 min at 0 °C. The mixture gradually turned black and was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure. The black residue and triethylammonium salt was removed by applying the crude product mixture to a column (3.0 cm x 17 cm) of flash silica gel and eluting with dichloromethane (~300 mL). The residue obtained by concentrating the dichloromethane eluate was further purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 9.8:0.2) to provide 773 mg (41%) of **59** as a white solid.

R_f = 0.31 (CH_2Cl_2/EtOAc, 9.5:0.5); mp: 90-91 °C; IR (neat): 2158, 1752, 1686, 1355, 1328, 1220, 1105, 1015, 973 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.68 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5 (*C*=O), 163.6 (O*C*=O), 72.7 (O*C*H_2).

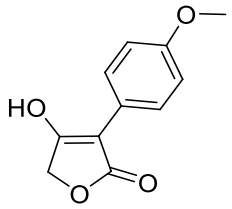
Insertion reactions of 59 and arenes:

General Procedure 1: To a solution of **59** in the aromatic compound (1.5 mL) was added the Rh(II) catalyst at room temperature. The reaction mixture was then placed in pre-heated oil bath at 100 °C. The mixture was heated until complete consumption of the diazotetronic acid (TLC), then cooled to room temperature and ethyl acetate (5 mL) was added. The suspension was extracted with saturated aqueous $NaHCO_3$ (3 x 2 mL). The unreacted aromatic compound was recovered by concentration of the organic layer. The combined aqueous extracts were acidified to pH ~3 with 2 N HCl and the suspension was extracted with ethyl acetate (4 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude product which was generally pure by ^1H NMR. If necessary, the crude product was purified by flash chromatography on silica gel.

General Procedure 2: To a suspension of **59** (1 equiv) in α,α,α-trifluorotoluene (2 mL) was added the aromatic compound (4 equiv) followed by the Rh(II) catalyst (1 mol%) at room temperature and the reaction mixture was placed in a pre-heated oil bath at 100 °C. The mixture was heated until complete consumption of **59** (TLC), then cooled to room temperature and ethyl acetate (5 mL) was added. The suspension was extracted with saturated aqueous $NaHCO_3$ (3 x 2 mL). The unreacted aromatic compound was recovered by concentration of the organic layer. The combined aqueous extracts were acidified to pH

~3 with 2N HCl and the suspension was extracted with ethyl acetate (4 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude product that was generally pure by ^{1}H NMR. If necessary, the crude product was purified by flash chromatography on silica gel.

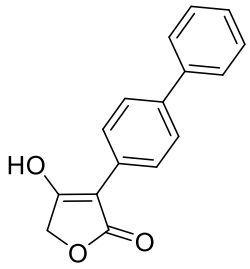
4-Hydroxy-3-(4-methoxyphenyl)furan-2(5*H*)-one (79):



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in anisole (1.5 mL) for 6 h according to General Procedure 1 provided, 78 mg (96%) of **79** as a white solid.

R_f = 0.39 (EtOAc/hexanes, 3:2); mp: 227-229 °C; IR (neat): 2952 (br), 2925 (br), 2692 (br), 1634, 1605, 1510, 1421, 1395, 1346, 1295, 1250, 1235, 1164, 1050, 1015, 955, 832 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.59 (br s, 1H, O*H*), 7.85 (d, 2H, *J* = 8.9 Hz, Ar*H*), 6.95 (d, 2H, *J* = 8.9 Hz, Ar*H*), 4.75 (s, 2H, OCH_2), 3.75 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.4 (*C*=O or C=*C*OH), 173.1 (*C*=O or C=*C*OH), 157.6 (ArC_{ipso}), 127.6 (2 × Ar*C*), 123.0 (ArC_{ipso}), 113.6 (2 × Ar*C*), 97.2 (*C*=COH), 66.0 (O*C*H_2), 55.0 (O*C*H_3); HRMS (ESI): *m/z* 206.0579 (206.0579 calc. for $C_{11}H_{10}O_4$, $(M)^+$) and 229.0470 (229.0477 calc. for $C_{11}H_{10}NaO_4$, $(M+Na)^+$).

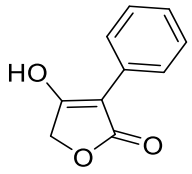
3-(Biphenyl-4-yl)-4-hydroxyfuran-2(5*H*)-one (80):



The reaction of **59** (50 mg, 0.39 mmol), biphenyl (244 mg, 1.58 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) for 5 h according to General Procedure 2 provided, after purification by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.7:0.3 to 9.5:0.5), 50 mg (51%) of **80** as a white solid.

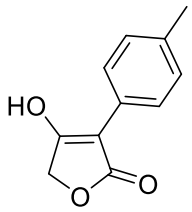
R_f = 0.26 (EtOAc/hexanes, 3:2); mp: 246-249 °C; IR (neat): 3035 (br), 2954, 2921, 2853 (br), 2664 (br), 1688, 1637, 1414, 1395, 1339, 1312, 1235, 1166, 1052, 1017, 957, 840 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.74-7.65 (m, 4H, Ar*H*), 7.51-7.42 (m, 2H, Ar*H*), 7.39-7.31 (m, 1H, Ar*H*), 4.79 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.6 (*C*=O or C=*C*OH), 173.0 (*C*=O or C=*C*OH), 139.8 (ArC_{ipso}), 137.7 (ArC_{ipso}), 129.9 (ArC_{ipso}), 128.9 (2 × Ar*C*), 127.3 (Ar*C*), 126.5 (2 × Ar*C*), 126.4 (2 × Ar*C*), 126.2 (2 × Ar*C*), 96.7 (*C*=COH), 66.2 (O*C*H_2); HRMS (CI): *m/z* 252.0785 (252.0786 calc. for $C_{16}H_{12}O_3$, $(M)^+$) and 275.0677 (275.0684 calc. for $C_{16}H_{12}NaO_3$, $(M+Na)^+$).

4-Hydroxy-3-phenylfuran-2(5*H*)-one (81):[28]



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in benzene (1.5 mL) for 15 h according to General Procedure 1 provided 66 mg (94%) of **81** as a yellow solid. Detailed spectroscopic data for **88** was given in chapter 2, page 157.

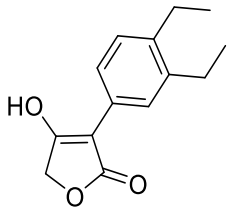
4-Hydroxy-3-*p*-tolylfuran-2(5*H*)-one (82):[28]



The reaction of **59** (100 mg, 0.790 mmol), $Rh_2(OAc)_4$ (3.5 mg, 7.9 x 10^{-3} mmol) in toluene (2.5 mL) for 76 h according to General Procedure 1 provided after purification by flash chromatography on silica gel (hexanes/EtOAc, 1:1 to 3:7), 93 mg (62%) of **82** as a white solid.

R_f = 0.26 (EtOAc/hexanes, 3:2); mp: 243-245 °C; IR (neat): 2921, 2859, 1717, 1651, 1601, 1515, 1433, 1393, 1336, 1312, 1162, 1020, 949, 822 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.81 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.18 (d, 2H, *J* = 8.1 Hz, Ar*H*), 4.75 (s, 2H, OCH_2), 2.29 (s, 3H, ArCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.5 (*C*=O or C=*C*OH), 173.0 (*C*=O or C=*C*OH), 135.4 (ArC_{ipso}), 128.6 (2 × Ar*C*), 127.7 (ArC_{ipso}), 126.1 (2 × Ar*C*), 97.2 (*C*=COH), 66.0 (OCH_2), 20.8 (ArCH_3).

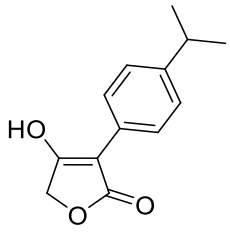
3-(3,4-Diethylphenyl)-4-hydroxyfuran-2(5*H*)-one (83):



The reaction of **59** (100 mg, 0.790 mmol), $Rh_2(CF_3CO_2)_4$ (5.2 mg, 7.9 x 10^{-3} mmol) in 1,2-diethylbenzene (2.5 mL) for 42 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexane/EtOAc, 3:2 to 2:3), 118 mg (64%) of **83** as a white solid.

R_f = 0.28 (hexanes/EtOAc, 1:1); mp: 180-183 °C; IR (neat): 2970, 2961, 2933, 2871, 2564 (br), 1588, 1439, 1381, 1370, 1343, 1058, 1044, 866, 830 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.62 (br s, 1H, O*H*), 7.70 (d, 1H, *J* = 1.9 Hz, Ar*H*), 7.64 (dd, 1H, *J* = 8.0, 1.9 Hz, Ar*H*), 7.14 (d, 1H, *J* = 8.0 Hz, Ar*H*), 4.75 (s, 2H, OCH_2), 2.60 (q, 2H, *J* = 7.5 Hz, CH_2CH$_3$), 2.59 (q, 2H, *J* = 7.5 Hz, CH_2CH$_3$), 1.16 (t, 3H, *J* = 7.5 Hz, CH$_2$CH_3), 1.15 (t, 3H, *J* = 7.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.1 (*C*=O or C=*C*OH), 173.0 (*C*=O or C=*C*OH), 140.7 (ArC_{ipso}), 139.4 (ArC_{ipso}), 128.0 (ArC_{ipso}), 127.9 (Ar*C*), 126.2 (Ar*C*), 124.1 (Ar*C*), 97.6 (*C*=COH), 65.9 (OCH_2), 25.0 (*C*H$_2$CH$_3$), 24.6 (*C*H$_2$CH$_3$), 15.4 (CH$_2$*C*H$_3$), 15.3 (CH$_2$*C*H$_3$); HRMS (APPI): *m/z* 232.1093 (232.1099 calc. for $C_{14}H_{16}O_3$, $(M)^+$) and 233.1166 (233.1178calc. for $C_{14}H_{17}O_3$, $(M+H)^+$)

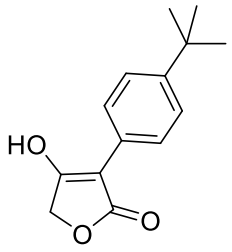
4-Hydroxy-3-(4-isopropylphenyl)furan-2(5*H*)-one (84):



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in cumene (1.5 mL) for 91 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.5:0.5 to 8.5:1.5), 28 mg (32%) of **84** as a pale-yellow solid.

R_f = 0.23 (CH_2Cl_2/CH_3OH, 9:1); mp: 132-134 °C; IR (neat): 2960, 2934, 2869, 2662 (br), 2600 (br), 1620, 1576, 1515, 1435, 1392, 1348, 1335, 1057, 1018, 960, 831 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.83 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.22 (d, 2H, *J* = 8.3 Hz, Ar*H*), 4.72 (s, 2H, OCH_2), 2.86 (septet, 1H, *J* = 6.8 Hz, C*H*(CH_3)$_2$), 1.20 (d, 6H, *J* = 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.2 (*C*=O or C=*C*OH), 173.2 (*C*=O or C=*C*OH), 146.1 (ArC_{ipso}), 128.3 (ArC_{ipso}), 126.2 (2 × Ar*C*), 125.9 (2 × Ar*C*), 96.8 (*C*=COH), 66.1 (OCH_2), 33.2 (*C*H(CH_3)$_2$), 23.9 (CH(*C*H_3)$_2$); HRMS (ESI): *m/z* 218.0944 (218.0943 calc. for $C_{13}H_{14}O_3$, $(M)^+$) and 241.0836 (241.0841 calc. for $C_{13}H_{14}NaO_3$, $(M+Na)^+$).

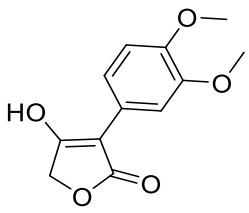
3-(4-*tert*-Butylphenyl)-4-hydroxyfuran-2(5*H*)-one (85):



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in *tert*-butylbenzene (1.5 mL) for 24 h according to General Procedure 1 provided, 87 mg (95%) of **85** as a white solid.

R_f = 0.29 (EtOAc/hexanes, 3:2); mp: 153-156 °C; IR (neat): 2959, 2657 (br), 2596 (br), 1697, 1599, 1581, 1517, 1434, 1393, 1343, 1314, 1064, 1016, 962, 840, 831 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.71 (br s, 1H, O*H*), 7.80 (d, 2H, *J* = 8.5 Hz, Ar*H*), 7.39 (d, 2H, *J* = 8.5 Hz, Ar*H*), 4.76 (s, 2H, OCH_2), 1.28 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.3 (*C*=O or C=*C*OH), 173.0 (*C*=O or C=*C*OH), 148.7 (ArC_{ipso}), 127.5 (ArC_{ipso}), 126.1 (2 × Ar*C*), 124.8 (2 × Ar*C*), 97.4 (*C*=COH), 66.0 (O*C*H_2), 34.2 (*C*(CH_3)$_3$), 31.1 (3 × *C*H_3); HRMS (APPI): *m/z* 232.1097 (232.1099 calc. for $C_{14}H_{16}O_3$, $(M)^+$) and 233.1173 (233.1178 calc. for $C_{14}H_{17}O_3$, $(M+H)^+$).

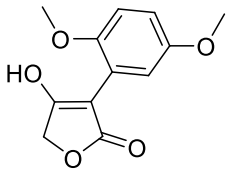
3-(3,4-Dimethoxyphenyl)-4-hydroxyfuran-2(5*H*)-one (86):[28]



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in 1,2-dimethoxybenzene (1.5 mL) for 11 h according to General Procedure 1 provided, 90 mg (96%) of **86** as a white solid.

R_f = 0.23 (CH_2Cl_2/CH_3OH, 9:1); mp: 207-209 °C; IR (neat): 2957 (br), 2935 (br), 2917 (br), 2681 (br), 1694, 1633 (br), 1584, 1518, 1400, 1344, 1322, 1259, 1236, 1145, 1024 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.65 (br s, 1H, O*H*), 7.57 (d, 1H, *J* = 1.9 Hz, Ar*H*), 7.49 (dd, 1H, *J* = 8.5, 1.9 Hz, Ar*H*), 6.96 (d, 1H, *J* = 8.5 Hz, Ar*H*), 4.75 (s, 2H, OCH_2), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.6 (*C*=O or C=*C*OH), 173.1 (*C*=O or C=*C*OH), 148.2 (ArC_{ipso}), 147.4 (ArC_{ipso}), 123.2 (ArC_{ipso}), 119.1 (Ar*C*), 111.6 (Ar*C*), 110.2 (Ar*C*), 97.3 (*C*=COH), 66.0 (O*C*H_2), 55.44 (O*C*H_3), 55.37 (O*C*H_3).

3-(2,5-Dimethoxyphenyl)-4-hydroxyfuran-2(5*H*)-one (87):

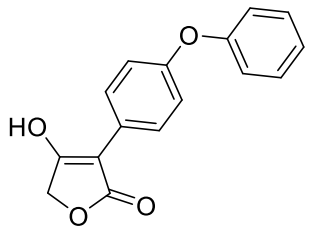


The reaction of **59** (50 mg, 0.39 mmol), 1,4-dimethoxybenzene (219 mg, 1.58 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) for 27 h according to General Procedure 2 provided, after purification by flash column chromatography on silica gel (hexane/EtOAc, 1:1 to 3:7), 51 mg (55%) of **87** as a brown solid.

R_f = 0.21 (hexanes/EtOAc, 7:3); mp: 133-136 °C; IR (neat): 3002, 2964, 2930, 2834, 1718,

1628 (br), 1506, 1470, 1408, 1321, 1253, 1227, 1207, 1155, 1024, 989, 870, 812 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.02 (br s, 1H, O*H*), 6.95 (d, 1H, *J* = 8.9 Hz, Ar*H*), 6.88 (dd, 1H, *J* = 8.9, 3.0 Hz, Ar*H*), 6.73 (d, 1H, *J* = 3.0 Hz, Ar*H*), 4.73 (s, 2H, OCH_2), 3.70 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.2 (*C*=O or C=*C*OH), 172.9 (*C*=O or C=*C*OH), 152.6 (ArC_{ipso}), 151.5 (ArC_{ipso}), 119.2 (ArC_{ipso}), 116.8 (Ar*C*), 113.5 (Ar*C*), 112.2 (Ar*C*), 97.2 (*C*=COH), 66.6 (O*C*H_2), 55.8 (O*C*H_3), 55.4 (O*C*H_3); HRMS (ESI): *m/z* 236.0686 (236.0685 calc. for $C_{12}H_{12}O_5$, $(M)^+$) and 259.0579 (259.0582 calc. for $C_{12}H_{12}NaO_5$, $(M+Na)^+$).

4-Hydroxy-3-(4-phenoxyphenyl)furan-2(5*H*)-one (88):

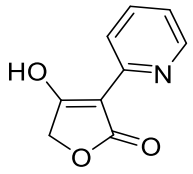


The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in diphenyl ether (1.5 mL) for 12 h according to General Procedure 1 provided, 99 mg (93%) of **88** as a white solid.

R_f = 0.20 (CH_2Cl_2/CH_3OH, 9:1); mp: 192-194 °C; IR (neat): 2933 (br), 2638 (br), 2588 (br), 1701, 1609, 1586, 1507, 1486, 1429, 1392, 1342, 1233, 1199, 1164, 1051, 1016, 842 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.50-12.25 (br s, 1H, O*H*), 7.92 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.44-7.34 (m, 2H, Ar*H*), 7.18-7.10 (m, 1H, Ar*H*), 7.07-6.98 (m, 4H, Ar*H*), 4.78 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.4 (*C*=O or C=*C*OH), 172.9 (*C*=O or

C=*C*OH), 156.8 (Ar*C*$_{ipso}$), 154.7 (Ar*C*$_{ipso}$), 130.0 (2 × Ar*C*), 127.9 (2 × Ar*C*), 125.9 (Ar*C*$_{ipso}$), 123.3 (Ar*C*), 118.5 (2 × Ar*C*), 118.4 (2 × Ar*C*), 96.8 (*C*=COH), 66.0 (O*C*H$_2$); HRMS (APPI): *m/z* 268.0739 (268.0736 calc. for $C_{16}H_{12}O_4$, $(M)^+$) and 269.0795 (269.0814 calc. for $C_{16}H_{13}O_4$, $(M+H)^+$).

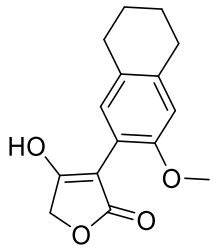
4-Hydroxy-3-(pyridin-2-yl)furan-2(5*H*)-one (89):



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in pyridine (1.5 mL) for 23 h according to General Procedure 1 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.7:0.3 to 9.5:0.5), 25 mg (36%) of **89** as a brown solid.

R_f = 0.38 (CH_2Cl_2/CH_3OH, 9:1); mp: 220-223 °C; IR (neat): 3084 (br) 2923 (br), 1712, 1621, 1574 (br), 1536, 1438, 1427, 1323, 1302, 1265, 1209, 1190, 1025, 1003, 952, 933 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.02 (br s, 1H, O*H*), 8.36 (d, 1H, *J* = 6.0 Hz, Ar*H*), 8.29 (d, 1H, *J* = 8.6 Hz, Ar*H*), 8.16 (ddd, 1H, *J* = 8.6, 7.2, 1.6 Hz, Ar*H*), 7.28 (ddd, 1H, *J* = 7.2, 6.0, 1.3 Hz, Ar*H*), 4.44 (s, 2H, OC*H*$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 192.8 (*C*=O), 173.6 (C=*C*OH), 148.9 (Ar*C*$_{ipso}$), 143.3 (Ar*C*), 137.8 (Ar*C*), 118.5 (Ar*C*), 117.5 (Ar*C*), 84.1 (*C*=COH), 70.1 (O*C*H$_2$); HRMS (ESI): *m/z* 177.0424 (177.0426 calc. for $C_9H_7NO_3$, $(M)^+$) and 200.0316 (200.0324 calc. for $C_9H_7NNaO_3$, $(M+Na)^+$).

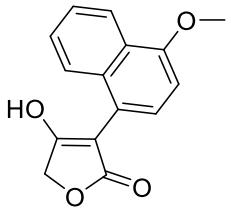
4-Hydroxy-3-(3-methoxy-5,6,7,8-tetrahydronaphthalen-2-yl)furan-2(5*H*)-one (90):



The reaction of **59** (50 mg, 0.39 mmol), 6-methoxy-1,2,3,4-tetrahydronaphthalene (0.25 mL, 1.6 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) for 27 h according to General Procedure 2 provided, after purification by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.7:0.3), 47 mg (46%) of **90** as a brown solid.

R_f = 0.26 (CH_2Cl_2/CH_3OH, 9.5:0.5); mp: 146-148 °C; IR (neat): 3002 (br), 2919 (br), 2853, 1756, 1717, 1634, 1605, 1461, 1450, 1404, 1311, 1252, 1235, 1197, 1157, 1106, 1050, 1028, 1014, 970, 850 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 11.82 (br s, 1H, O*H*), 6.81 (s, 1H, Ar*H*), 6.68 (s, 1H, Ar*H*), 4.71 (s, 2H, OCH_2), 3.67 (s, 3H, OCH_3), 2.77-2.67 (br m, 2H, ArCH_2), 2.66-2.56 (br m, 2H, ArCH_2), 1.77-1.65 (br m, 4H, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.8 (*C*=O or C=*C*OH), 173.2 (*C*=O or C=*C*OH), 155.1 (ArC_{ipso}), 137.2 (ArC_{ipso}), 131.4 (Ar*C*), 127.7 (ArC_{ipso}), 115.8 (ArC_{ipso}), 111.2 (Ar*C*), 97.4 (*C*=COH), 66.6 (OCH_2), 55.2 (OCH_3), 29.1 (CH_2), 27.9 (CH_2), 23.0 (CH_2), 22.7 (CH_2); HRMS (ESI): *m/z* 260.1052 (260.1049 calc. for $C_{15}H_{16}O_4$, $(M)^+$) and 283.0940 (283.0946 calc. for $C_{15}H_{16}NaO_4$, $(M+Na)^+$).

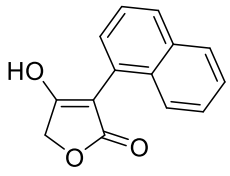
4-Hydroxy-3-(4-methoxynaphthalen-1-yl)furan-2(5*H*)-one (91):



The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in 1-methoxynaphthalene (1.5 mL) for 18 h according to General Procedure 1 provided after purification by flash chromatography on silica gel (EtOAc/hexanes, 1:1-7:3), 88 mg (87%) of **91** as a white solid.

R_f = 0.23 (hexanes/EtOAc, 1:1); mp: 155-157 °C; IR (neat): 2930 (br), 2716 (br), 2673 (br), 1644, 1580, 1427, 1406, 1368, 1341, 1319, 1269, 1241, 1068, 1024, 822 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.30 (br s, 1H, O*H*), 8.25-8.14 (m, 1H, Ar*H*), 7.74-7.65 (m, 1H, Ar*H*), 7.58-7.45 (m, 2H, Ar*H*), 7.32 (d, 1H, *J* = 7.9 Hz, Ar*H*), 7.01 (d, 1H, *J* = 7.9 Hz, Ar*H*), 4.90 (s, 2H, OCH_2), 3.99 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.8 (*C*=O or C=*C*OH), 173.7 (*C*=O or C=*C*OH), 154.5 (ArC_{ipso}), 132.1 (ArC_{ipso}), 128.6 (Ar*C*), 126.2 (Ar*C*), 125.6 (Ar*C*), 125.0 (Ar*C*), 124.8 (ArC_{ipso}), 121.5 (ArC_{ipso}), 119.2 (ArC_{ipso}), 104.0 (Ar*C*), 98.8 (*C*=COH), 66.7 (O*C*H_2), 55.5 (O*C*H_3); HRMS (ESI): *m/z* 256.0734 (256.0736 calc. for $C_{15}H_{12}O_4$, $(M)^+$) and 279.0626 (279.0633 calc. for $C_{15}H_{12}NaO_4$, $(M+Na)^+$).

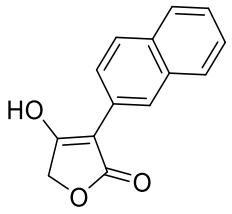
4-Hydroxy-3-(naphthalen-1-yl)furan-2(5*H*)-one (92):



The reaction of **59** (50 mg, 0.39 mmol), naphthalene (203 mg, 1.58 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) for 22 h according to General Procedure 2 provided, after purification by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH, 0.3:9.7 to 0.5:9.5), 50 mg (56%) of **92** as a white solid and 16 mg (18%) of **93** as a pale-yellow solid.

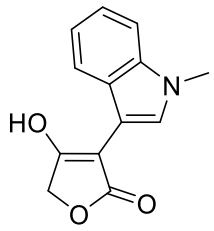
R_f = 0.22 (hexanes/EtOAc, 1:1); mp: 146-148 °C; IR (neat): 2922, 2853, 1706, 1648, 1629, 1613, 1572, 1467, 1434, 1397, 1314, 1258, 1214, 1169, 1047, 1014, 936, 800 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.45 (br s, 1H, O*H*), 8.00-7.88 (m, 2H, Ar*H*), 7.81-7.72 (m, 1H, Ar*H*), 7.59-7.45 (m, 3H, Ar*H*), 7.40 (d, 1H, *J* = 6.8 Hz, Ar*H*), 4.92 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.3 (*C*=O or C=*C*OH), 173.5 (*C*=O or C=*C*OH), 133.3 (ArC_{ipso}), 131.3 (ArC_{ipso}), 128.3 (Ar*C*), 128.2 (Ar*C*), 127.9 (Ar*C*), 127.5 (ArC_{ipso}), 125.8 (3×Ar*C*), 125.4 (Ar*C*), 98.9 (*C*=COH), 66.9 (O*C*H_2); HRMS (APPI): *m/z* 226.0621 (226.0630 calc. for $C_{14}H_{10}O_3$, $(M)^+$) and 227.0689 (227.0708 calc. for $C_{14}H_{11}O_3$, $(M+H)^+$).

4-Hydroxy-3-(naphthalen-2-yl)furan-2(5*H*)-one (93):



R_f = 0.21 (hexanes/EtOAc, 1:1); mp: 180-182 °C; IR (neat): 2955, 2922, 2852, 2725 (br), 1699, 1631, 1556, 1439, 1415, 1331, 1053, 1023, 821 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.49 (s, 1H, Ar*H*), 8.22 (dd, 1H, *J* = 8.6, 1.6 Hz, Ar*H*), 7.90-7.80 (m, 3H, Ar*H*), 7.51-7.38 (m, 2H, Ar*H*), 4.69 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.4 (*C*=O or C=*C*OH), 173.8 (*C*=O or C=*C*OH), 133.0 (ArC_{ipso}), 131.1 (ArC_{ipso}), 129.6 (ArC_{ipso}), 127.7 (Ar*C*), 127.3 (Ar*C*), 127.1 (Ar*C*), 125.9 (Ar*C*), 125.1 (Ar*C*), 124.5 (Ar*C*), 123.4 (Ar*C*), 95.1 (*C*=COH), 66.7 (O*C*H_2);); HRMS (APPI): *m/z* 226.0640 (226.0630 calc. for $C_{14}H_{10}O_3$, $(M)^+$) and 244.1087 (244.0974 calc. for $C_{14}H_{14}NO_3$, $(M+NH_4)^+$).

4-Hydroxy-3-(1-methyl-1H-indol-3-yl)furan-2(5*H*)-one (94):

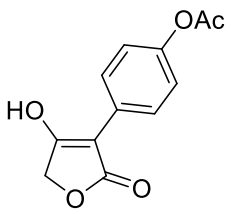


Prepared by the reaction of **59** (50 mg, 0.39 mmol), $Rh_2(OAc)_4$ (1.7 mg, 3.9 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) for 17 h according to General Procedure 2 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and

the residue was directly purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1 to 7:3) to provide 84 mg (92%) of **94** as a crimson solid.

R_f = 0.32 (EtOAc/hexanes, 3:2); mp: 157-159 °C; IR (neat): 3050, 2925 (br), 2695 (br), 2649, 1644 (br), 1611, 1540, 1408, 1331, 1193, 1075, 1018, 809 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.14 (br s, 1H, O*H*), 7.95 (br d, 1H, *J* = 8.0, Hz, Ar*H*), 7.61 (s, 1H, Ar*H*), 7.41 (br d, 1H, *J* = 8.0, Hz, Ar*H*), 7.16 (ddd, 1H, *J* = 8.1, 6.9, 1.0 Hz, Ar*H*), 7.03 (ddd, 1H, *J* = 8.1, 6.9, 1.0 Hz, Ar*H*), 4.81 (s, 2H, OCH_2), 3.81 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.5 (*C*=O or C=*C*OH), 170.5 (*C*=O or C=*C*OH), 136.2 (ArC_{ipso}), 128.1 (Ar*C*), 126.0 (ArC_{ipso}), 121.8 (Ar*C*), 121.2 (Ar*C*), 118.6 (Ar*C*), 109.5 (Ar*C*), 103.4 (ArC_{ipso}), 95.1 (*C*=COH), 66.5 (O*C*H_2), 32.5 (N*C*H_3); HRMS (ESI): *m/z* 229.0739 (229.0739 calc. for $C_{13}H_{11}NO_3$, $(M)^+$) and 230.0811 (230.0817 calc. for $C_{13}H_{12}NO_3$, $(M+H)^+$).

4-(4-Hydroxy-2-oxo-2,5-dihydrofuran-3-yl)phenyl acetate (95):

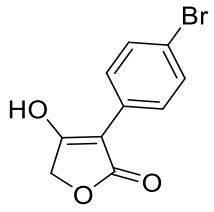


Prepared by the reaction of **59** (50 mg, 0.39 mmol), phenyl acetate (0.20 mL, 1.6 mmol) and $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) for 66 h according to General Procedure 2 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by

flash chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.5:0.5 to 9:1) to provide 49 mg (53%) of **95** as a white solid.

R_f = 0.26 (EtOAc/hexanes, 3:2); mp: 142-145 °C; IR (neat): 3411 (br), 2937 (br), 2657 (br), 2592 (br), 1737, 1649 (br), 1604, 1429, 1397, 1367, 1340, 1218, 1192, 1165, 1049, 1014, 959, 913 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.75-11.75 (br s, 1H, O*H*), 7.94 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.13 (d, 2H, *J* = 8.6 Hz, Ar*H*), 4.78 (s, 2H, OCH_2), 2.27 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.1 (*C*=O or C=*C*OH), 172.9 (*C*=O or C=*C*OH), 169.3 (CH_3CO_2Ar), 148.6 (ArC_{ipso}), 128.2 (ArC_{ipso}), 127.2 (2 × Ar*C*), 121.5 (2 × Ar*C*), 96.7 (*C*=COH), 66.1 (OCH_2), 20.8 (COCH_3); HRMS (APPI): *m/z* 234.0523 (234.0528 calc. for $C_{12}H_{10}O_5$, $(M)^+$) and 252.0861 (252.0872 calc. for $C_{12}H_{14}NO_5$, $(M+NH_4)^+$).

3-(4-Bromophenyl)-4-hydroxyfuran-2(5*H*)-one (96):[28]

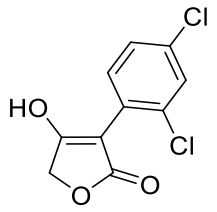


The reaction of **59** (50 mg, 0.39 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in bromobenzene (1.5 mL) for 46 h according to General Procedure 1 provided, 68 mg (67%) of **96** as a light brown solid.

R_f = 0.23 (EtOAc/hexanes, 3:2); mp: 269-271 °C; IR (neat): 2971 (br), 2651 (br), 2555 (br), 1693, 1567 (br), 1431, 1385, 1342, 1298, 1055, 1017, 955, 870, 821 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.91 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.57 (d, 2H, *J* = 8.6 Hz, Ar*H*), 4.77 (s,

2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.0 (*C*=O or C=*C*OH), 172.7 (*C*=O or C=*C*OH), 131.0 (2 × Ar*C*), 130.0 (ArC_{ipso}), 128.0 (2 × Ar*C*), 119.0 (ArC_{ipso}), 96.1 (*C*=COH), 66.2 (O*C*H_2).

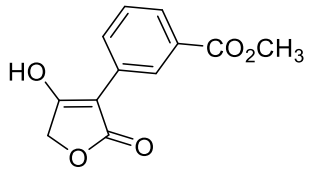
3-(2,4-Dichlorophenyl)-4-hydroxyfuran-2(5*H*)-one (97):[28]



Prepared by the reaction of **59** (50 mg, 0.39 mmol), $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) and 1,3-dichlorobenzene (1.5 mL) for 74 h according to General Procedure 1, but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.5:0.5 to 9:1) to provide 41 mg (42%) of **97** as a yellow solid.

R_f = 0.35 (CH_2Cl_2/CH_3OH, 9:1); mp: 206-209 °C; IR (neat): 2916, 2848, 2651, 2596, 1712, 1697, 1606, 1573, 1542, 1428, 1341, 1048, 1027, 1016, 962, 864 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.67 (d, 1H, *J* = 2.1 Hz, Ar*H*), 7.46 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 7.32 (d, 1H, *J* = 8.3 Hz, Ar*H*), 4.81 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.0 (*C*=O or C=*C*OH), 172.2 (*C*=O or C=*C*OH), 134.6 (ArC_{ipso}), 133.6 (Ar*C*), 133.0 (ArC_{ipso}), 128.7 (Ar*C*), 128.1 (ArC_{ipso}), 127.1 (Ar*C*), 97.3 (*C*=COH), 67.0 (O*C*H_2).

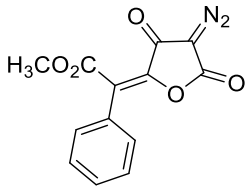
Methyl 3-(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)benzoate (98):



Prepared by the reaction of **59** (50 mg, 0.39 mmol), methyl benzoate (0.20 mL, 1.6 mmol) and $Rh_2(CF_3CO_2)_4$ (2.6 mg, 3.9 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) for 77 h according to General Procedure 2 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH, 9.5:0.5 to 9:1) to provide, 48 mg (52%) of **98** as a white solid.

R_f = 0.15 (CH_2Cl_2/CH_3OH, 9.5:0.5); mp: 122-125 °C; IR (neat): 2955, 2920, 2660 (br), 2597 (br), 1711, 1633, 1603, 1576, 1419, 1275, 1226, 1172, 1048, 1028, 960 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.68 (t, 1H, *J* = 1.4 Hz, Ar*H*), 8.29 (dt, 1H, *J* = 7.8, 1.4 Hz, Ar*H*), 7.72 (dt, 1H, *J* = 7.8, 1.4 Hz, Ar*H*), 7.46 (t, 1H, *J* = 7.8 Hz, Ar*H*), 4.61 (s, 2H, OCH_2), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.7 (*C*=O or C=*C*OH), 173.8 (*C*=O or C=*C*OH), 166.6 (*C*O_2CH_3), 132.8 (ArC_{ipso}), 129.7 (Ar*C*), 129.3 (ArC_{ipso}), 128.3 (Ar*C*), 125.8 (Ar*C*), 125.6 (Ar*C*), 93.6 (*C*=COH), 66.9 (O*C*H_2), 52.0 (O*C*H_3); HRMS (APPI): *m/z* 234.0535 (234.0528 calc. for $C_{12}H_{10}O_5$, $(M)^+$) and 252.0853 (252.0872 calc. for $C_{12}H_{14}NO_5$, $(M+NH_4)^+$).

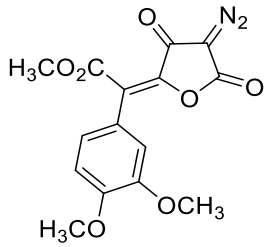
(*E*)-Methyl 2-(4-diazo-3,5-dioxodihydrofuran-2(3*H*)-ylidene)-2-phenylacetate (103):



To a solution of **59** (80 mg, 0.63 mmol) and methyl 2-oxo-2-phenylacetate (125 mg, 0.760 mmol) in CH_2Cl_2 (2 mL) was added $TiCl_4$ (0.20 mL, 1.9 mmol) at -78 °C and the solution was stirred for 30 min and triethylamine (0.27 mL, 1.9 mmol) was added. The mixture stirred at -78 °C for 30 min and then at 0 °C for 5 h and saturated aqueous NH_4Cl (~2 mL) was added followed by cold water (~1 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 4:1) to provide 106 mg (61%) of **103** as a light brown solid.

R_f = 0.27 (hexanes/EtOAc, 4:1); mp: 155-157 °C; IR (neat): 2951, 2923, 2853, 2165, 1787, 1729, 1697, 1621, 1359, 1325, 1298, 1273, 1225, 1201, 1067, 1043, 1028, 997, 974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72-7.62 (m, 2H, Ar*H*), 7.49-7.38 (m, 3H, Ar*H*), 3.95 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3 (*C*=O), 165.7 (*C*=O), 159.3 (*C*=O), 140.3 (ArC_{ipso}), 130.7 (Ar*C*), 129.54 (2 × Ar*C*), 129.46 (O-*C*=C), 129.0 (2 × Ar*C*), 120.0 (Ph-*C*-CO_2CH_3), 53.4 (O*C*H$_3$); HRMS (APPI): *m/z* 272.0438 (272.0433 calc. for $C_{13}H_8N_2O_5$, $(M)^+$) and 273.0509 (273.0511 calc. for $C_{13}H_9N_2O_5$, $(M+H)^+$).

(*E*)-Methyl 2-(4-diazo-3,5-dioxodihydrofuran-2(3*H*)-ylidene)-2-(3,4-dimethoxyphenyl)acetate (105):

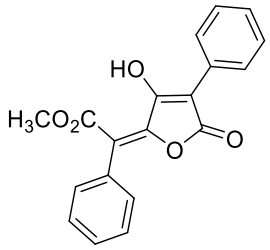


To a solution of **59** (80 mg, 0.63 mmol) and methyl 2-(3,4-dimethoxyphenyl)-2-oxoacetate[3] (171 mg, 0.760 mmol) in CH_2Cl_2 (2 mL) was added $TiCl_4$ (0.20 mL, 1.9 mmol) at -78 °C and the solution was stirred for 30 min and triethylamine (0.27 mL, 1.9 mmol) was added. The mixture was stirred at -78 °C for 40 min saturated aqueous NH_4Cl (~2 mL) was added. The mixture was then warmed to room temperature and cold water (~1 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 7.5:2.5) to provide 124 mg (59%) of **105** as a yellow solid.

R_f = 0.20 (hexanes/EtOAc, 7:3); mp: 108-110 °C; IR (neat): 2952, 2923, 2851, 2161, 1792, 1735, 1693, 1616, 1587, 1513, 1444, 1425, 1363, 1290, 1238, 1215, 1150, 1068, 1048, 1030, 1012, 933, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 1H, *J* = 2.2 Hz, Ar*H*), 7.25 (dd, 1H, *J* = 8.6, 2.2 Hz, Ar*H*), 6.90 (d, 1H, *J* = 8.6 Hz, Ar*H*), 3.96 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2 (*C*=O), 165.9 (*C*=O), 159.4 (*C*=O), 151.3 (ArC_{ipso} or O-*C*=C), 149.1 (ArC_{ipso} or O-*C*=C), 138.9 (ArC_{ipso} or O-*C*=C), 123.9 (Ar*C*), 122.0 (ArC_{ipso} or O-C=*C*), 120.2 (ArC_{ipso} or O-C=*C*), 112.2

(Ar*C*), 111.1 (Ar*C*), 56.0 (2 × O*C*H$_3$), 53.4 (O*C*H$_3$); HRMS (APPI): *m/z* 332.0645 (332.0645 calc. for $C_{15}H_{12}N_2O_7$, $(M)^+$) and 333.0717 (333.0723calc. for $C_{15}H_{13}N_2O_7$, $(M+H)^+$).

(*E*)-Methyl 2-(3-hydroxy-5-oxo-4-phenylfuran-2(5*H*)-ylidene)-2-phenylacetate (2, Vuplinic acid):[29]

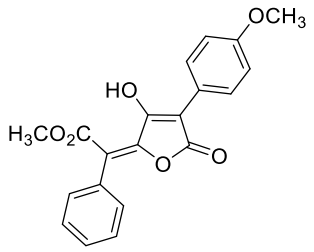


The reaction of **103** (60 mg, 0.22 mmol), $Rh_2(OAc)_4$ (1.0 mg, 2.2 x 10^{-3} mmol) in benzene (1.5 mL) for 24 h according to General Procedure 1 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (hexanes/EtOAc, 4:1 to 7:3) to provide 65 mg (91%) of **2** as a yellow solid.

R_f = 0.51 (hexanes/EtOAc, 7:3); mp: 149-151 °C; IR (neat): 3032, 3021, 2962, 2922, 2852, 2503, 2453, 1767, 1677, 1608, 1587, 1429, 1317, 1300, 1275, 1260, 1156, 1066, 949, 903, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.77 (s, 1H, O*H*), 8.16-8.09 (m, 2H, Ar*H*), 7.49-7.23 (m, 8H, Ar*H*), 3.88 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7 (*C*=O or C=*C*OH), 165.9 (*C*=O or C=*C*OH), 160.3 (*C*=O or C=*C*OH), 154.9 (*C*=O or C=*C*OH or C-O-*C*=C), 132.0 (ArC_{ipso}), 130.0 (2 × Ar*C*), 129.0 (ArC_{ipso}), 128.6 (Ar*C*), 128.5 (2 × Ar*C*),

128.4 (Ar*C*), 128.2 (2 × Ar*C*), 127.9 (2 × Ar*C*), 115.8 (Ph-*C*-CO_2CH_3), 105.2 (HO-C=*C*), 54.5 (O*C*H_3).

(*E*)-Methyl-2-(3-hydroxy-4-(4-methoxyphenyl)-5-oxofuran-2(5*H*)-ylidene)-2-phenylacetate (4, Pinastric acid):[30]

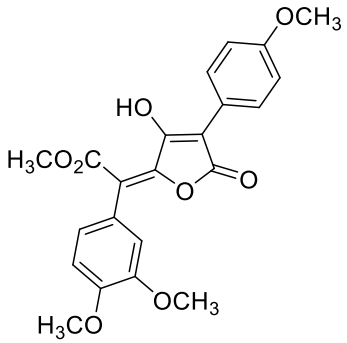


Prepared by the reaction of **103** (60 mg, 0.22 mmol), anisole (96 μL, 0.88 mmol) and $Rh_2(CF_3CO_2)_4$ (1.4 mg, 2.2 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) for 7 h according to General Procedure 2 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (hexanes/EtOAc, 1.7:0.3 to 3:3) to provide 54 mg (70%) of **4** as an orange solid.

R_f = 0.41 (hexanes/EtOAc, 7:3); mp: 201-203 °C; IR (neat): 3017, 2958, 2931, 2838, 2510, 2459, 1755, 1671, 1594, 1569, 1513, 1436, 1416, 1304, 1276, 1250, 1187, 1155, 1060, 1022, 955, 841 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.58 (s, 1H, O*H*), 8.12 (d, 2H, *J* = 9.1 Hz, Ar*H*), 7.46-7.35 (m, 3H, Ar*H*), 7.30-7.21 (m, 2H, Ar*H*), 6.97 (d, 2H, *J* = 9.1 Hz, Ar*H*), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7 (*C*=O or C=*C*OH), 166.1 (*C*=O or C=*C*OH), 159.5 (*C*=O or C=*C*OH), 158.6 (C-O-*C*=C or ArC_{ipso}), 155.0 (C-O-*C*=C or ArC_{ipso}), 132.1 (ArC_{ipso}), 130.0 (2 × Ar*C*), 129.4 (2 × Ar*C*),

128.5 (Ar*C*), 128.1 (2 × Ar*C*), 121.6 (ArC_{ipso}), 115.2 (Ph-*C*-CO_2CH_3), 113.9 (2 × Ar*C*), 105.3 (HO-C=*C*), 55.3 (O*C*H_3), 54.4 (O*C*H_3).

(*E*)-Methyl 2-(3,4-dimethoxyphenyl)-2-(3-hydroxy-4-(4-methoxyphenyl)-5-oxofuran-2(5*H*)-ylidene)acetate (110):[10a]

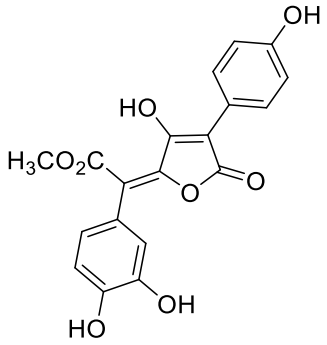


Prepared by the reaction of **105** (120 mg, 0.360 mmol), anisole (0.160 mL, 1.44 mmol) and $Rh_2(CF_3CO_2)_4$ (2.4 mg, 3.6 x 10^{-3} mmol) in α,α,α-trifluorotoluene (3 mL) for 9 h according to General Procedure 2 but the acid-base workup procedure was not followed. The reaction mixture was concentrated and the residue was directly purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 10:0 to 9.9:0.1) to provide 105 mg (70%) of **110** as an orange-yellow solid.

R_f = 0.26 (CH_2Cl_2/EtOAc, 9.9:0.1); mp: 157-159 °C; IR (neat): 3003, 2956, 2929, 2838, 2557, 1765, 1674, 1592, 1513, 1441, 1411, 1303, 1248, 1215, 1181, 1141, 1063, 1024, 996, 948, 908, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.56 (s, 1H, O*H*), 8.12 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.96 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.90 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.83 (dd, 1H, *J* = 8.3, 1.9 Hz, Ar*H*), 6.77 (d, 1H, *J* = 1.9 Hz, Ar*H*), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8 (*C*=O), 166.2

(*C*=O), 159.5 (Ar*C*$_{ipso}$ or O-*C*=C or *C*=O), 158.6 (Ar*C*$_{ipso}$ or O-*C*=C or *C*=O), 155.0 (Ar*C*$_{ipso}$ or O-*C*=C or *C*=O), 149.3 (Ar*C*$_{ipso}$), 148.5 (Ar*C*$_{ipso}$), 129.3 (2 × Ar*C*), 124.4 (Ar*C*$_{ipso}$ or O-C=*C*), 122.9 (Ar*C*), 121.7 (Ar*C*$_{ipso}$ or O-C=*C*), 115.1 (Ar*C*$_{ipso}$ or O-C=*C*), 113.9 (2 × Ar*C*), 113.3 (Ar*C*), 110.7 (Ar*C*), 105.2 (HO-C=*C*), 56.1 (O*C*H$_3$), 55.9 (O*C*H$_3$), 55.3 (O*C*H$_3$), 54.4 (O*C*H$_3$); HRMS (APPI): *m/z* 412.1155 (412.1158 calc. for $C_{22}H_{20}O_8$, $(M)^+$) and 413.1227 (413.1236 calc. for $C_{22}H_{21}O_8$, $(M+H)^+$).

(*E*)-Methyl 2-(3,4-dihydroxyphenyl)-2-(3-hydroxy-4-(4-hydroxyphenyl)-5-oxofuran-2(5*H*)-ylidene)acetate (6, Methyl isoxerocomate):[31]



To a solution of compound **110** (45 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 0.76 mL, 0.76 mmol,) over 5 min at 0 °C. The mixture was then warmed to room temperature and stirred for 3 h. It was then cooled to 0 °C and cold water (2 mL) was added. The resulting mixture was extracted with ethyl acetate (4 x 3 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 3:2 to 3:7) to provide 27 mg (72%) of **6** as a yellow-orange solid.

R_f = 0.31 (EtOAc/hexanes, 3:2); mp: 213-216 °C; IR (neat): 3323 (br), 2956, 2921, 2851, 2600 (br), 1741, 1702, 1675, 1597, 1513, 1433, 1263, 1176, 1149, 1115, 1100, 1062, 999, 911, 836, 811 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6): δ 13.71 (br, 1H, O*H*), 8.69 (br, 1H, O*H*), 8.16 (br, 1H, O*H*), 8.04 (br, 1H, O*H*), 8.00 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.93 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.91 (d, 1H, *J* = 2.1 Hz, Ar*H*), 6.87 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.75 (dd, 1H, *J* = 8.2, 2.1 Hz, Ar*H*), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, acetone-d_6): δ 173.0 (*C*=O or C=*C*OH), 167.0 (*C*=O or C=*C*OH), 159.7 (C=*C*OH or *C*=O), 158.4 (ArC_{ipso} or O-*C*=C), 154.4 (ArC_{ipso} or O-*C*=C), 146.4 (ArC_{ipso} or O-*C*=C), 145.3 (ArC_{ipso} or O-*C*=C), 130.1 (2 × Ar*C*), 125.0 (ArC_{ipso} or O-C=*C*), 123.1 (Ar*C*), 121.8 (ArC_{ipso} or O-C=*C*), 118.4 (Ar*C*), 116.5 (ArC_{ipso} or O-C=*C*), 116.2 (2 × Ar*C*), 115.6 (Ar*C*), 105.1 (HO-C=*C*), 54.7 (O*C*H_3).

3.7 References

1 Wolffe, L., Schwabe, C. *Liebigs. J. Ann. Chem.* **1896**, *291*, 226.

2. Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157

3. (a) Zaghouani, M.; Nay, B. *Nat. Prod. Reps.* **2016**, *33*, 540. (b) Schobert, R.; Schlenck, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203

4. Yao, T.-T.; Cheng, J.-L.; Xu, B.-R.; Zhang, M.-Z.; Hu, Y.-Z.; Zhao, J.-H.; Dong, X.-W. *RSC Adv.* **2015**, *5*, 49195.

5. (a) Chrusciel R.; Strohbach J. W. *Curr. Top. Med. Chem.* **2004**, *4*, 1097. (b) Romines, K. R.; Chrusciel, R. A. *Curr. Med. Chem.* **1995**, *2*, 825.

6. Lopez, M. D.; Quinoa, E; Riguera, R. *J. Nat. Prod.* **1994**, *57*, 992.

7. Foden, F. R.; McCormick, J.; O'Mant, D. M. *J. Med.Chem.* **1975**, *18*, 199

8. Duncan, C. J. G.; Cuendet, M.; Fronczek, F. R.; Pezzuto, J. M.; Mehta, R. G.; Hamann, M. T.; Ross, S. A. *J. Nat. Prod.* **2003**, *66*, 103.

9. (a) Gruber, G.; Kerschensteiner, L.; Marumoto, R.; Steglich, W. *Z. Naturforsch.* **2013**, *68b*, 675. (b) van der Sar, S. A.; Blunt, J. W.; Cole, A. L. J.; Din, L. B.; Munro, M. H. G.*J. Nat. Prod.* **2005**, *68*, 1799.

10. (a) Edwards, R. L.; Gill, M. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1529. (b) Steffan, B.; Steglich, W. *Angew. Chem.* **1984**, *96*, 435.

11. Jerris, P. J.; Wovkulich, P. M.; Smith, A. B., III *Tetrahedron Lett.* **1979**, *19*, 4517

12. Ramage, R.; Griffiths, G. J.; Sweeney, J. N. A. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 1547

13. (a) Gedge, D. R.; Pattenden, G.; Smith, A. G. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 2127. (b) Pattenden, G.; Turvill, M. W.; Chorlton, A. P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2357

14. Ahmed, Z.; Langer, P. *J. Org. Chem*. **2004**, *69*, 3753.

15. (a) Heurtaux, B.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2005**, *70*, 1474.

(b) Pattenden, G.; Pegg, N. A.; Kenyon, R. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2363.

16. Willis, C.; Bodio, E.; Bourdreux, Y.; Billaud, C.; Le Gall, T. *Tetrahedron Lett.* **2007**, *8*, 6421.

17. Mallinger, A.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2009***, 74,* 1124

18. (a) Yang, W.; Liu, J.; Zhang, H. *Tetrahedron Lett.* **2010**, *51*, 4874. (b) Xiao, Z.-P.; He, X.-B.; Peng, Z.-Y.; Xiong, T.-J.; Peng, J.; Chen, L.-H.; Zhu, H.-L. *Bioorg. Med. Chem.* **2011**, *19*, 1571.

19. (a) Studies on O-H bond insertion: Stachel, H. D.; Poschenrieder, H.; Redlin, J.; Schachtner, J.; Zeitler, K. *Liebigs Ann. Chem.* **1994**, 129. Application in heterocycle synthesis: (b) Rostovskii, N. V.; Novikov, M. S.; Khlebnikov, A. F.; Korneev, S. M.; Yufit, D. S. *Org. Biomol. Chem.* **2013**, *11*, 5535. (c) Murphy, P. V.; O'Sullivan, T. J.; Kennedy, B. D.; Geraghty, N. W. A. *J. Chem. Soc. Perkin Trans. 1*, **2000**, *13*, 2121.

20. Wen Ai, W.; Yang, X; Wu, Y.; Wang, X.; Li, Y.; Yaxi Yang, Y.; Zhou, B. *Chem. Eur. J.* **2014**, *20*, 17653. (d) Yu, X.-Z.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 5444.

21. Review: (a) Caballero, A.; Díaz-Requejo, M. M.; Fructos, M. R.; Olmos, A.; Urbano, J.; Pérez, P. J. *Dalton Trans.* **2015**, *44*, 20295 (b) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 9817. (c) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (d) Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700. (e) Yang, J.-M.; Cai, Y.; Zhu, S.-F.; Zhou, Q.-L. *Org. Biomol. Chem.* **2016**, *14*, 5516. (f) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, 6719. (g) Ma, B.; Wu, Z.; Huang, B.; Liu, L.; Zhang, J. *Chem. Commun.* **2016**, *52*, 9351. (h) Yu, Z.; Qiu, H.; Liu, L.; Zhang, J. *Chem. Commun.* **2016**, *52*, 2257. (i) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem. Int. Ed.* **2014**, *53*, 13098. (j) Cao, Z.-Y.; Zhao, Y.-L.; Zhou, J. *Chem. Commun*. **2016**, *52*, 2537. (k) Zhai, C.; Xing, D.; Jing, C.; Zhou, J.; Wang, C.; Wang, D.; Hu, W. *Org. Lett.* **2014**, *16*, 2934. (l) Magar, K. B. S.; Edison, T. N. J. I.; Lee, Y. R. *Org. Biomol. Chem.* **2016**, *14*, 7313. (m) Best, D.; Jean, M.; van der Weghe, P. *J. Org. Chem.* **2016**, *81*, 7760. (n) Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112. (o) Rosenfeld, M. J.; Shankar, B. K. R.; Schechter, H. *J. Org. Chem.* **1988**, *53*, 2699. (p) Maryanoff, B. *J. Org. Chem.* **1982**, *47*, 3000.

22. Hoffman, R. V.; Schechter, H. *J. Am. Chem. Soc.* **1978**, *100*, 7934.

23. Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.

24. The structural assignment **89** and **91** is based on the similarity of the aromatic region resonances in their ^{1}H NMR spectra with those of structurally related compounds. (a) Baraldi, P. G.; Romagnoli, R.; Pavani, M. G.; Nuñez, M.; Tabrizi, M. A.; Shryock, J.

C.; Leung, E.; Moorman, A. R.; Uluoglu, C.; Iannotta, V.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2003**, *46*, 794. (b) Korsager, S.; Taaning, R. F.; Skrydstrup, T. *J. Am. Chem. Soc.* **2013**, *135*, 2891.

25. (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (b) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415.

26. (a) Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 4951. (b) Lerche, H.; König, D.; Severin, T. *Chem. Ber.* **1974**, *107*, 1509.

27. Yang, M.; Webb, T. R.; Livant, P. *J. Org. Chem.* **2001**, *66*, 4945.

28. Wang, X.-D.; Wei, W.; Wang, P.-F.; Yi, L.-C.; Shi, W.-K.; Xie, Y.-X.; Wua, L.-Z.; Tang, N.; Zhu, L.-S.; Peng, J.; Liu, C.; Li, X.-H.; Tang, Shi.; Xiao, Z.-P.; Zhu, H.-L. *Bioorg. Med. Chem.* **2015**, *23*, 4860.

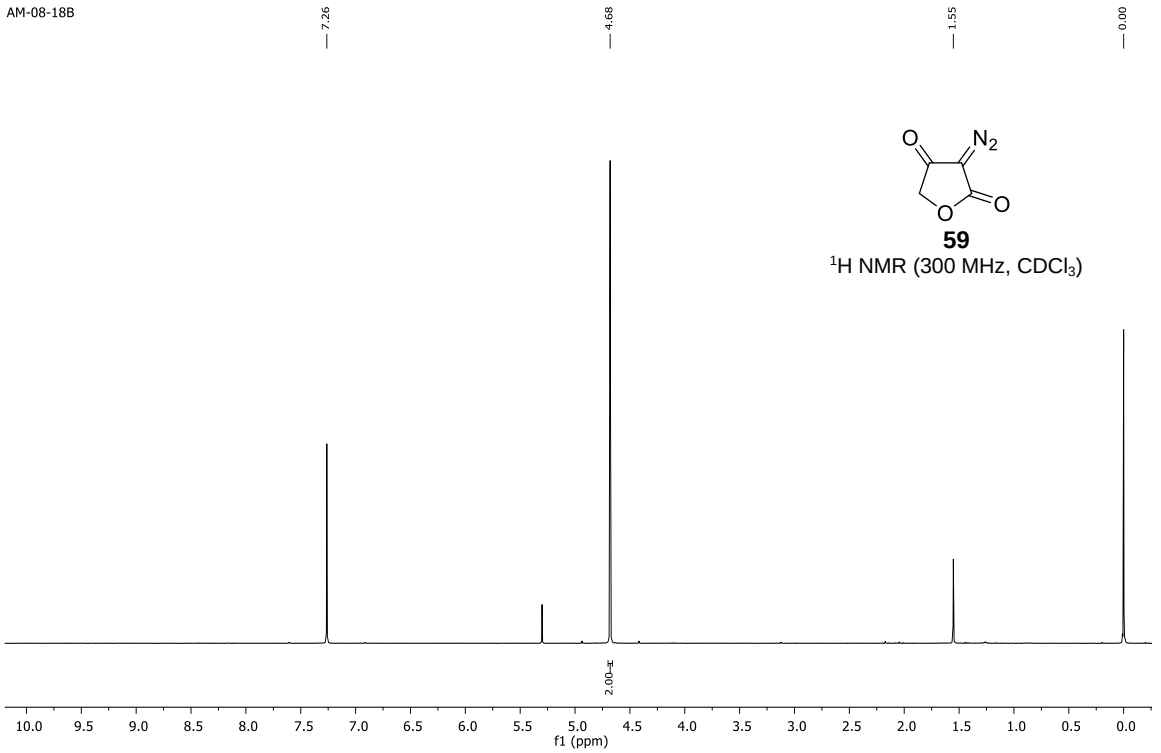
29. Bourdreux, Y.; Bodio, E.; Willis, C.; Billaud, C.; Gall, T. L.; Mioskowski, C. *Tetrahedron* **2008**, *64*, 8930.

30. Ahmed, Z.; Langer, P. *Tetrahedron* **2005,** *61*, 2055.

31. Gruber, G.; Kerschensteiner, L.; Steglich, W. *Z. Naturforsch.* **2014**, *69b*, 432.

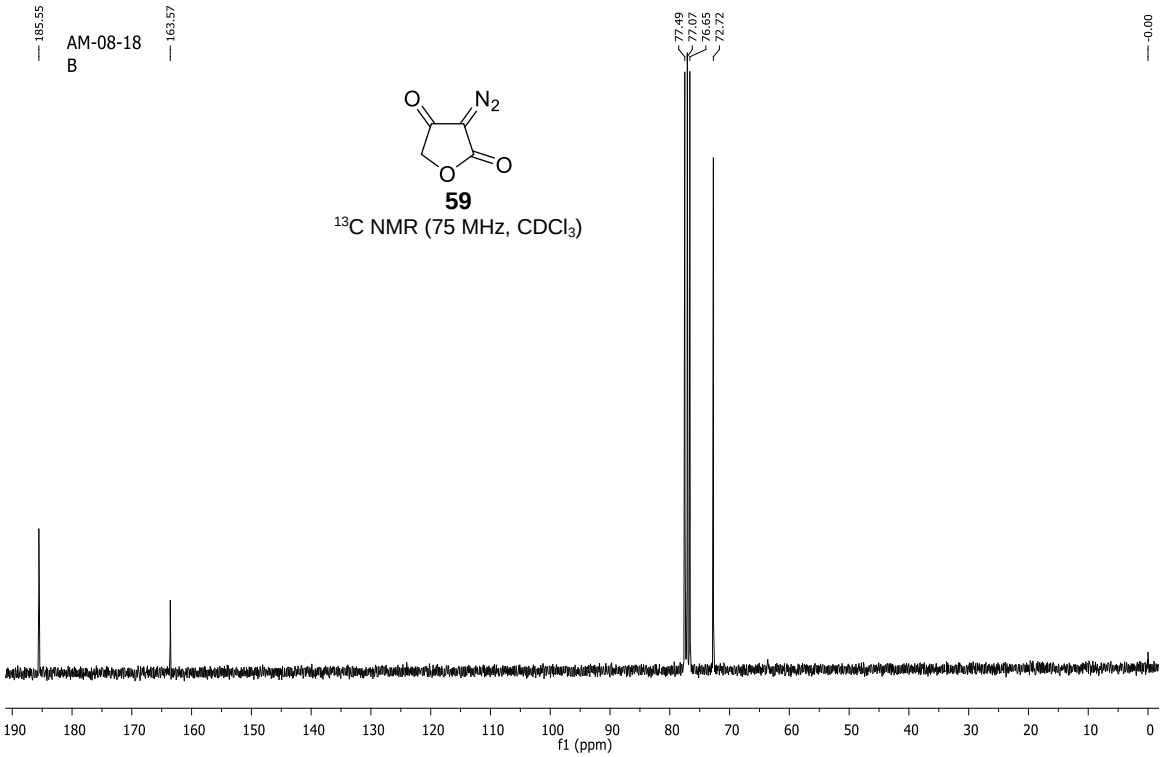
32.

3.8 Selected ^{1}H NMR and ^{13}C NMR Spectra



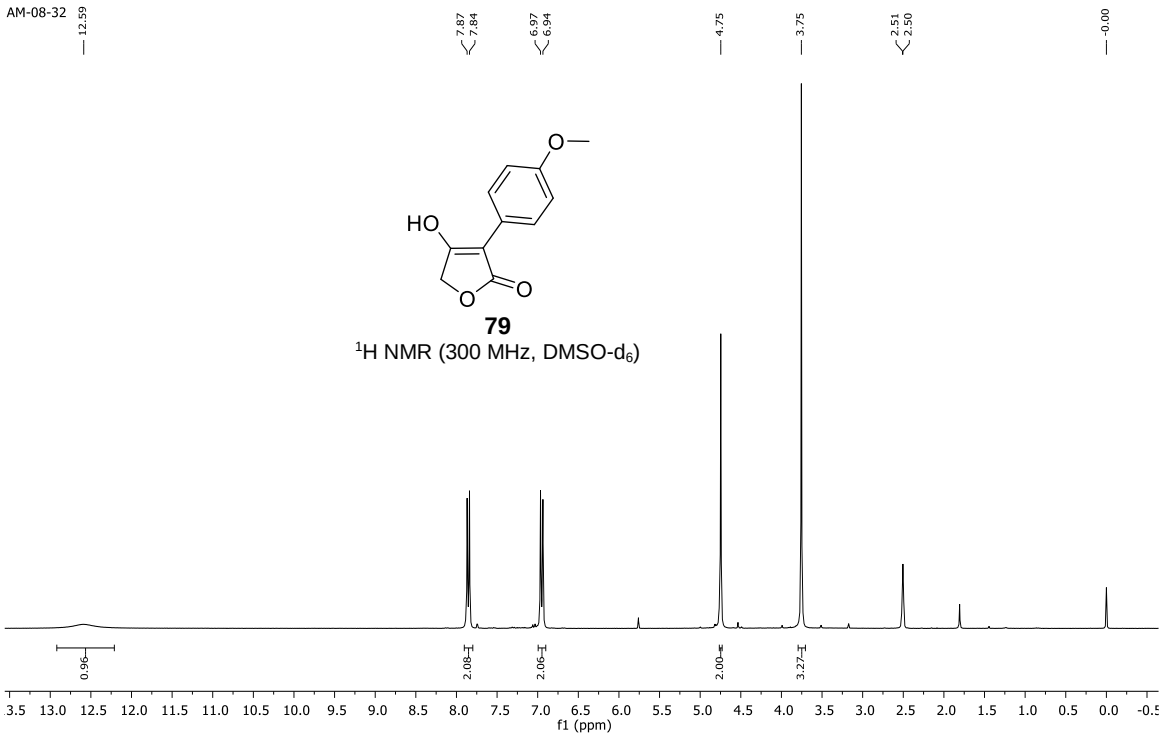
59

^{1}H NMR (300 MHz, $CDCl_3$)



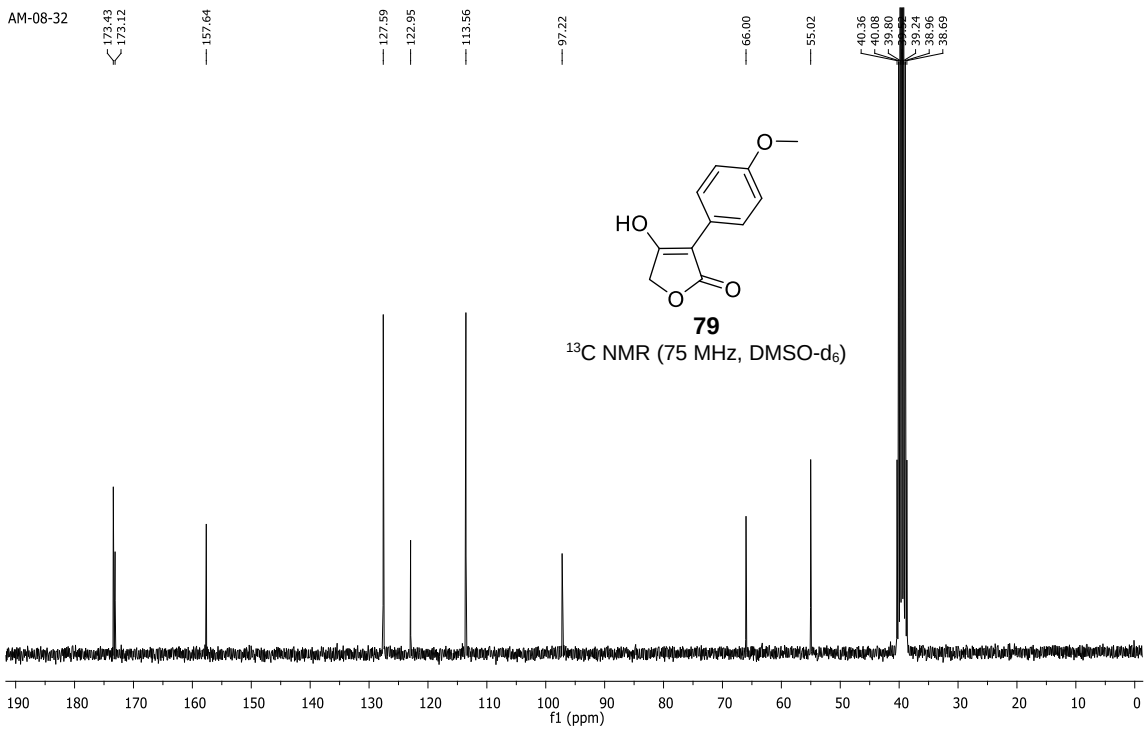
59

^{13}C NMR (75 MHz, $CDCl_3$)



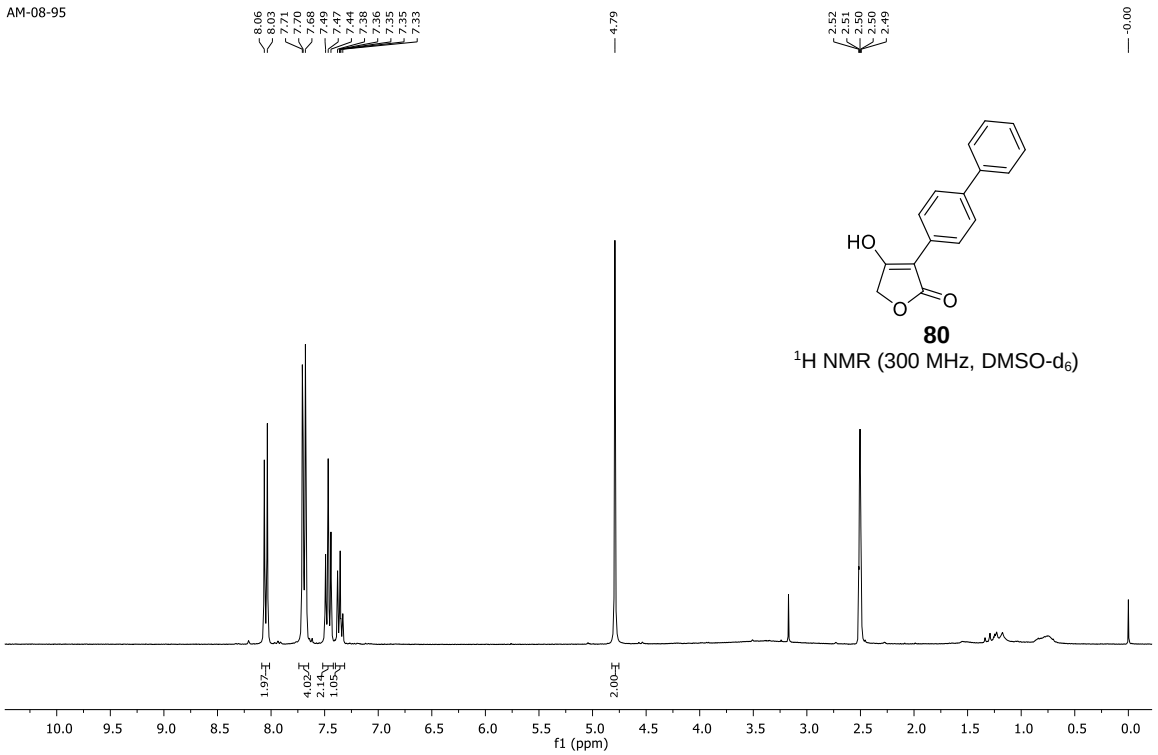
79

^{1}H NMR (300 MHz, DMSO-d_6)



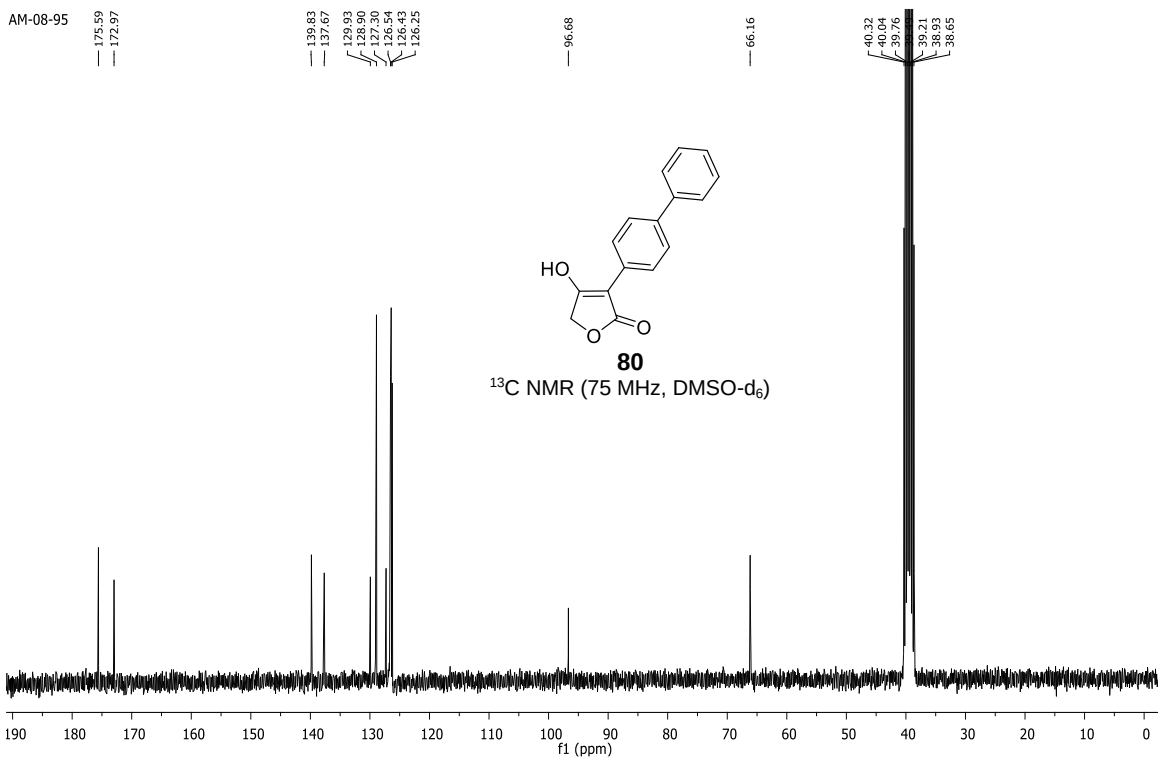
79

^{13}C NMR (75 MHz, DMSO-d_6)



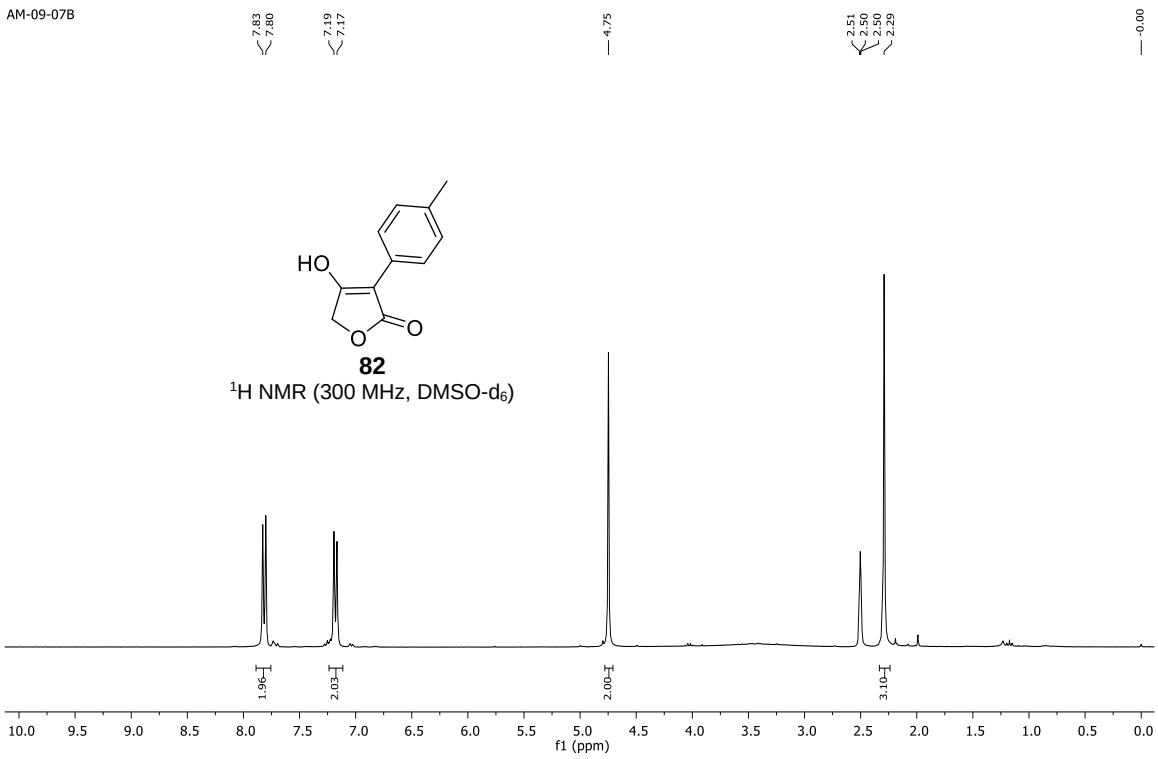
80

^{1}H NMR (300 MHz, DMSO-d_6)



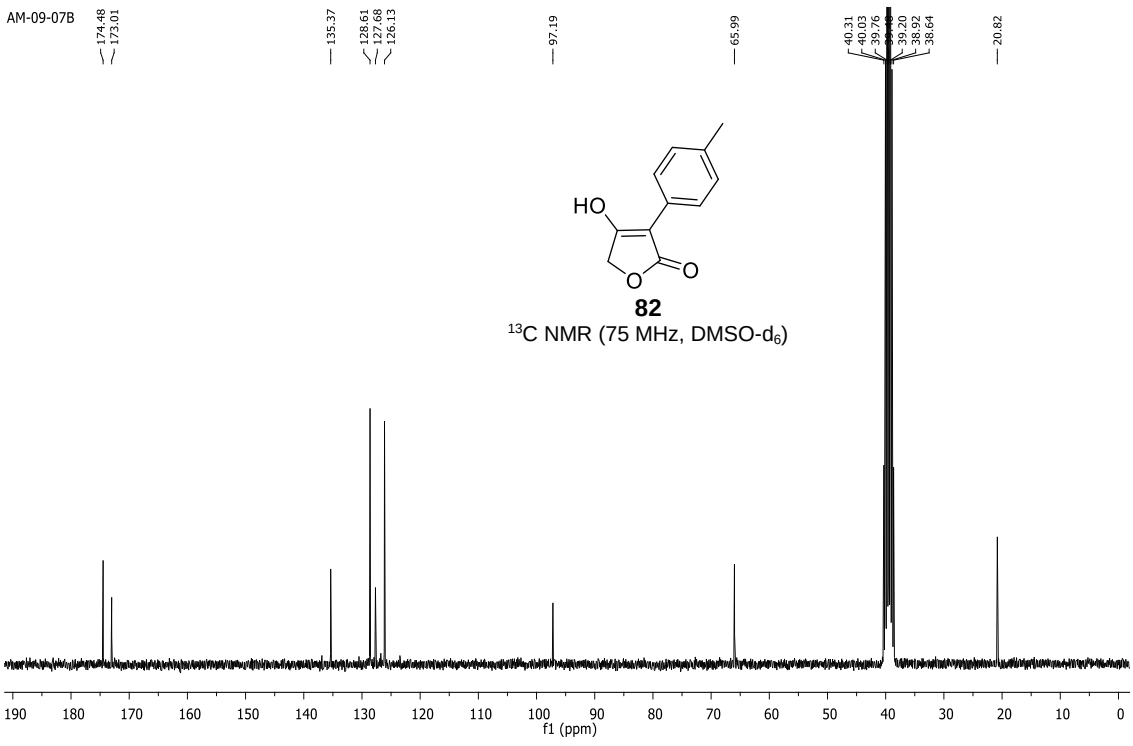
80

^{13}C NMR (75 MHz, DMSO-d_6)



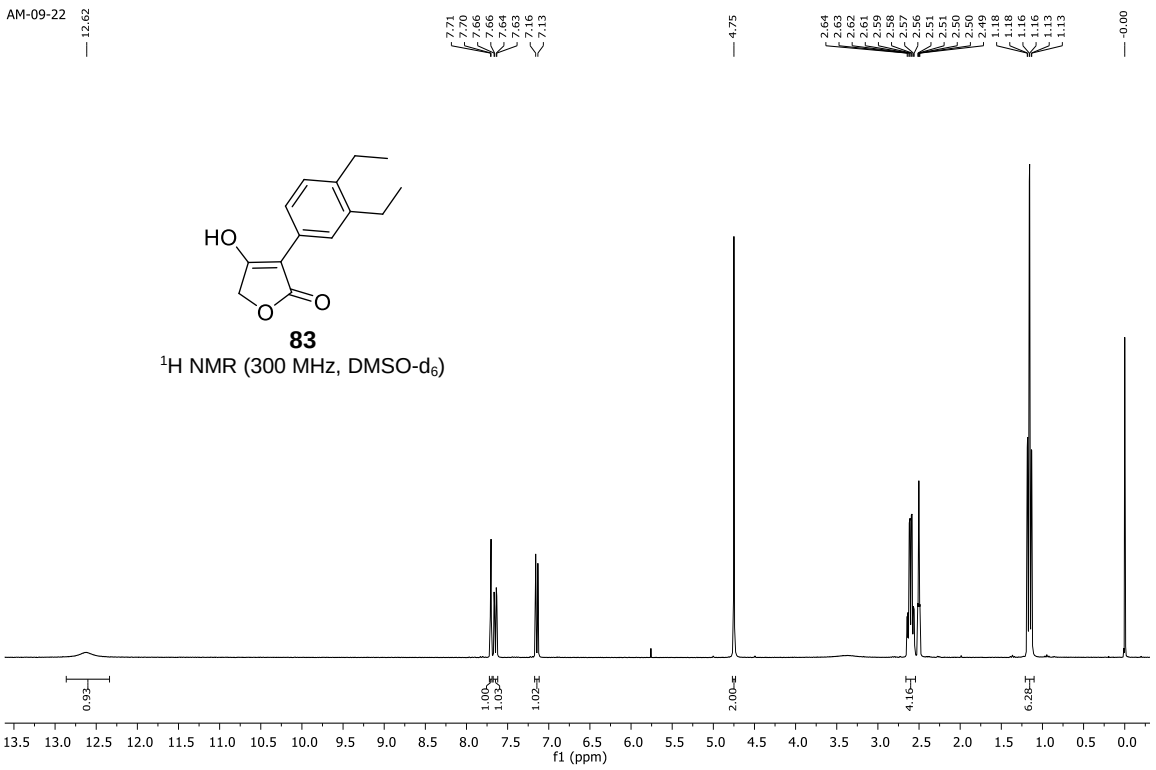
82

^{1}H NMR (300 MHz, DMSO-d_6)



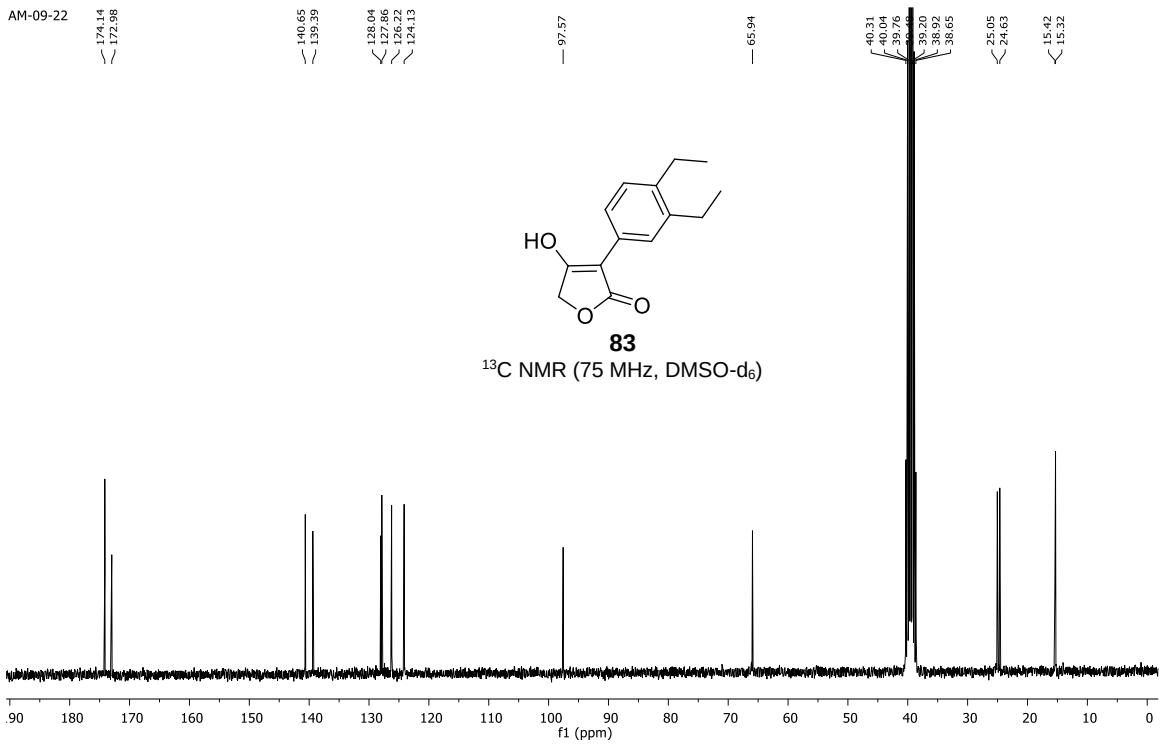
82

^{13}C NMR (75 MHz, DMSO-d_6)



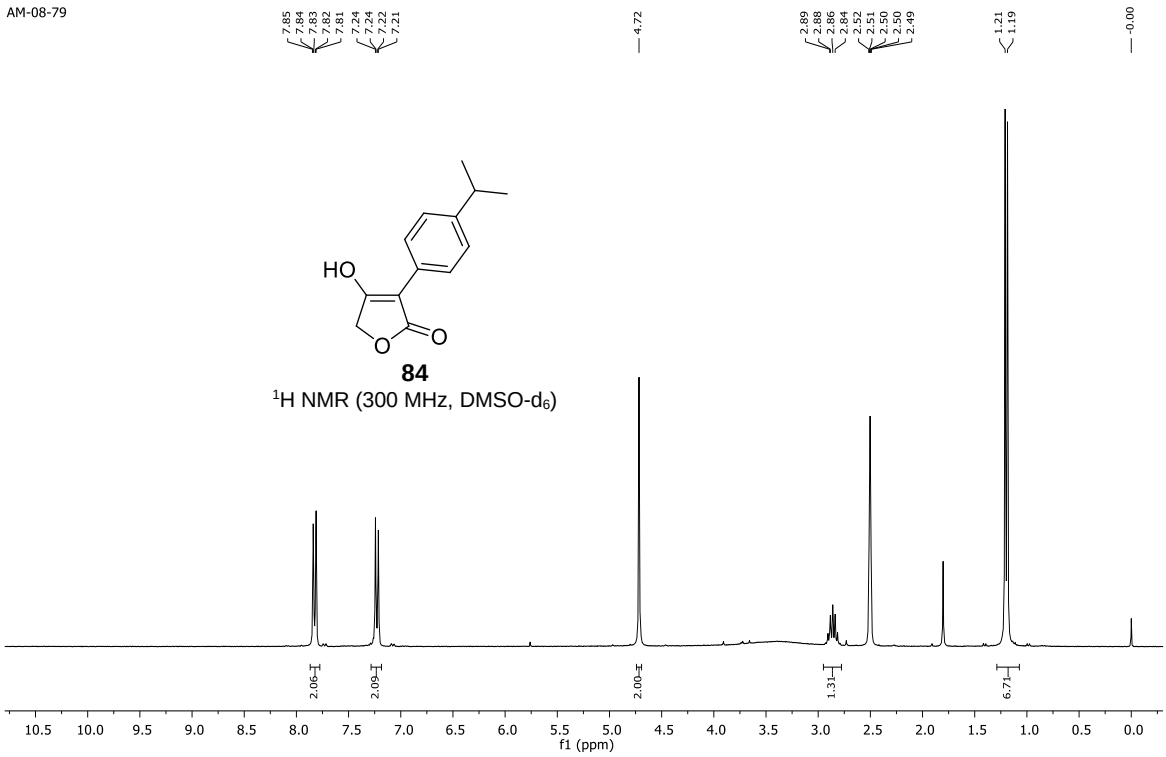
83

^{1}H NMR (300 MHz, DMSO-d_6)



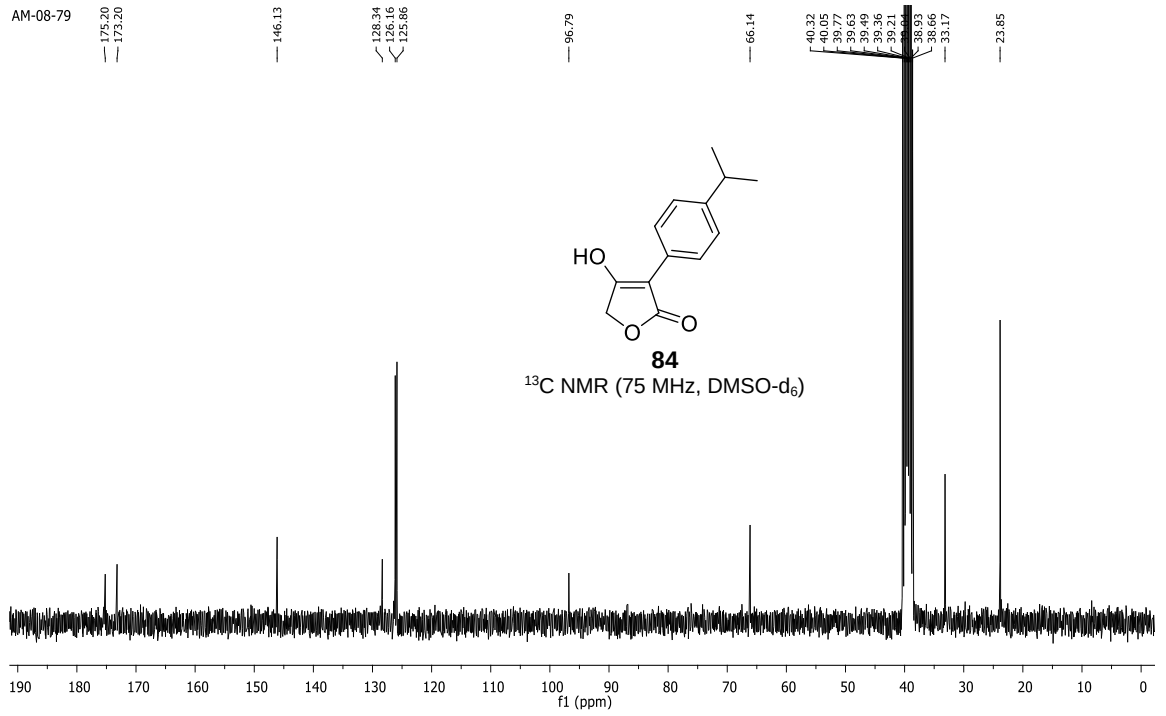
83

^{13}C NMR (75 MHz, DMSO-d_6)



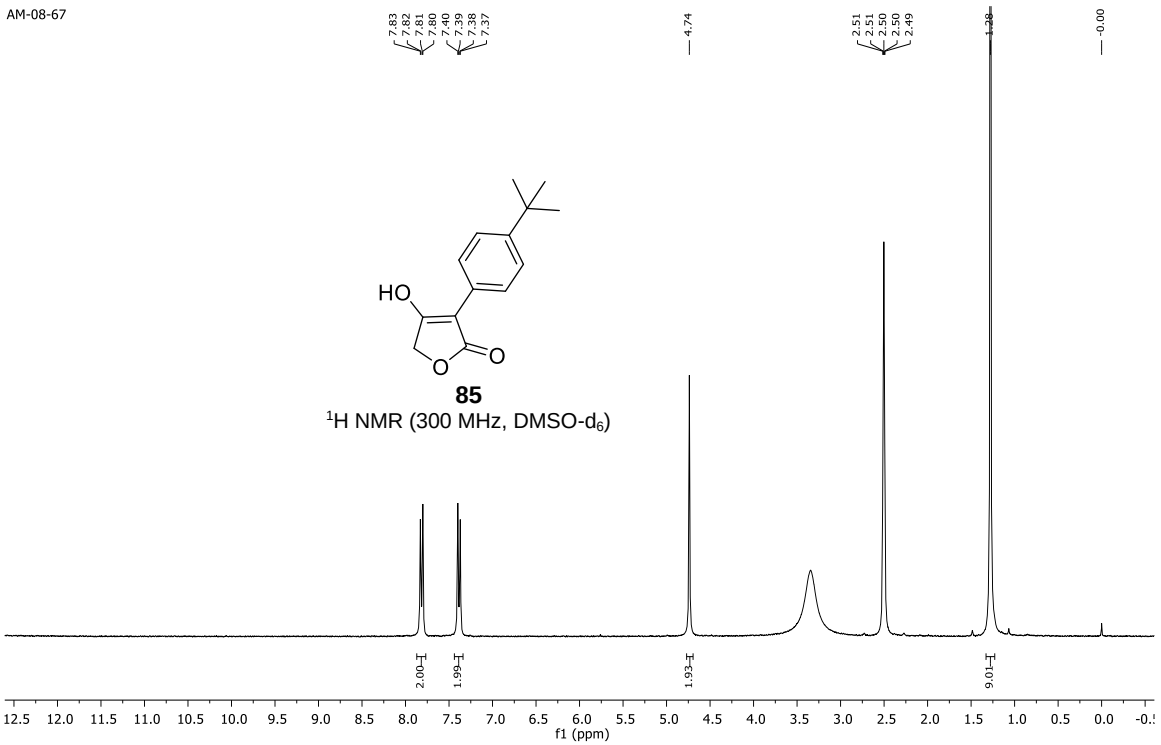
84

^{1}H NMR (300 MHz, DMSO-d_6)



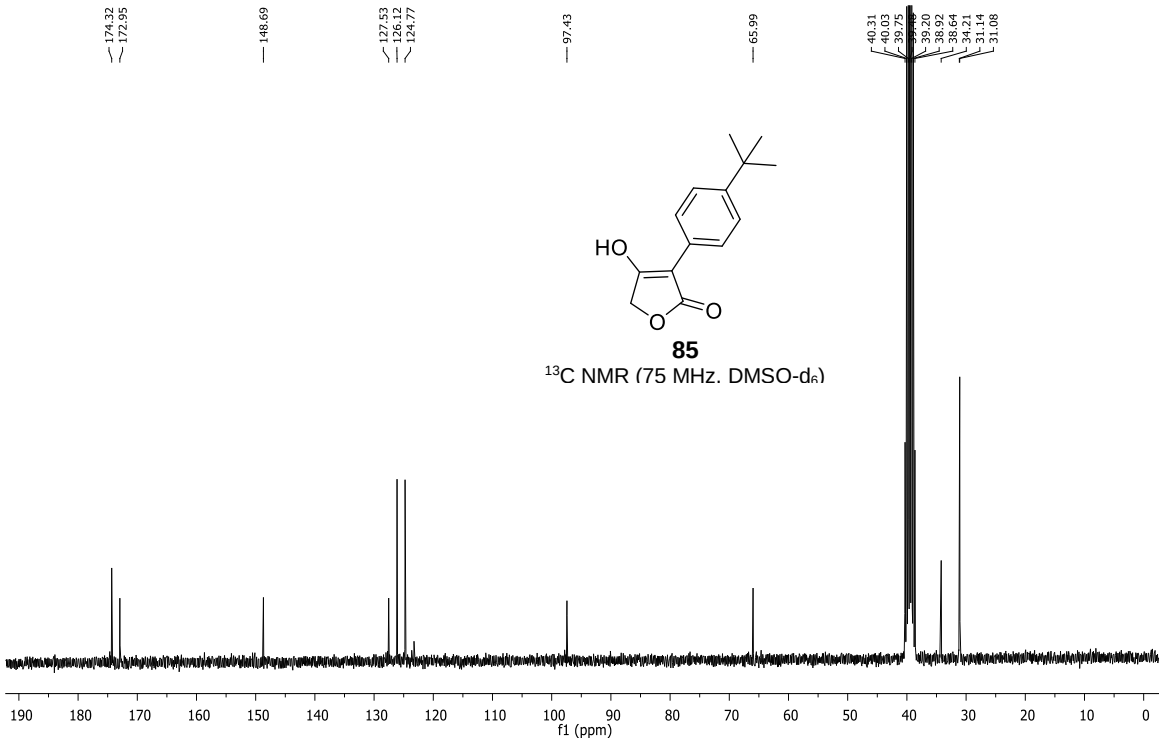
84

^{13}C NMR (75 MHz, DMSO-d_6)



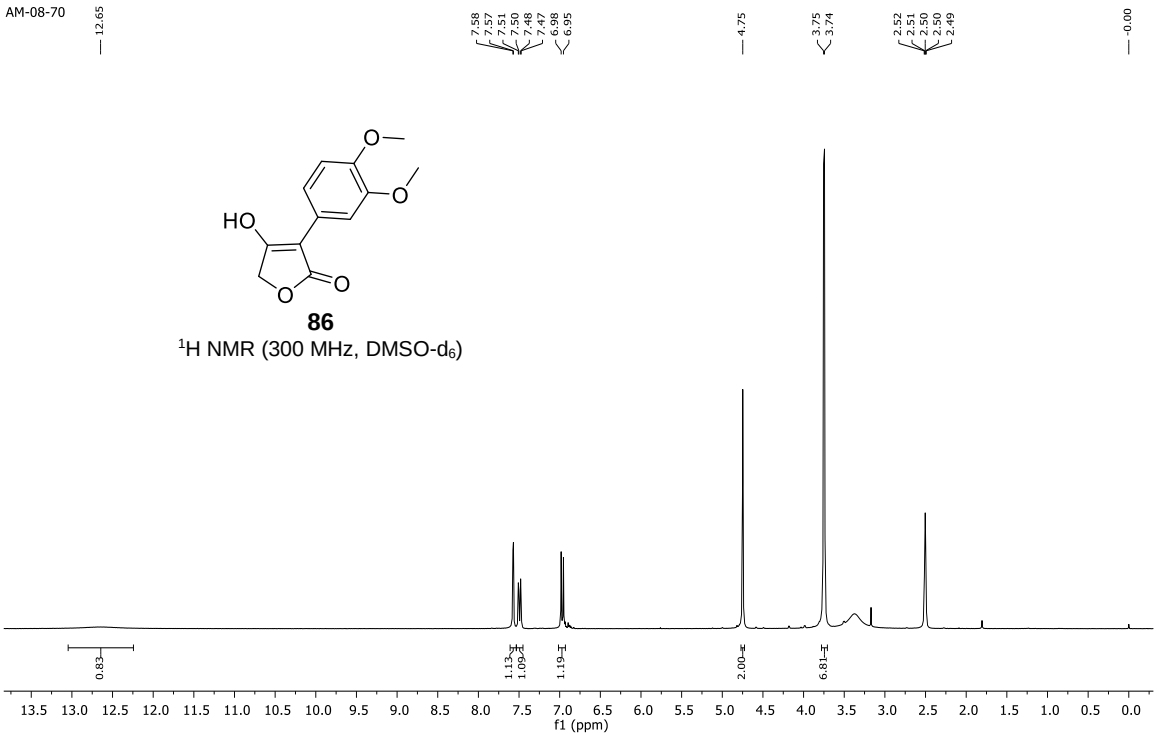
85

^{1}H NMR (300 MHz, DMSO-d_6)



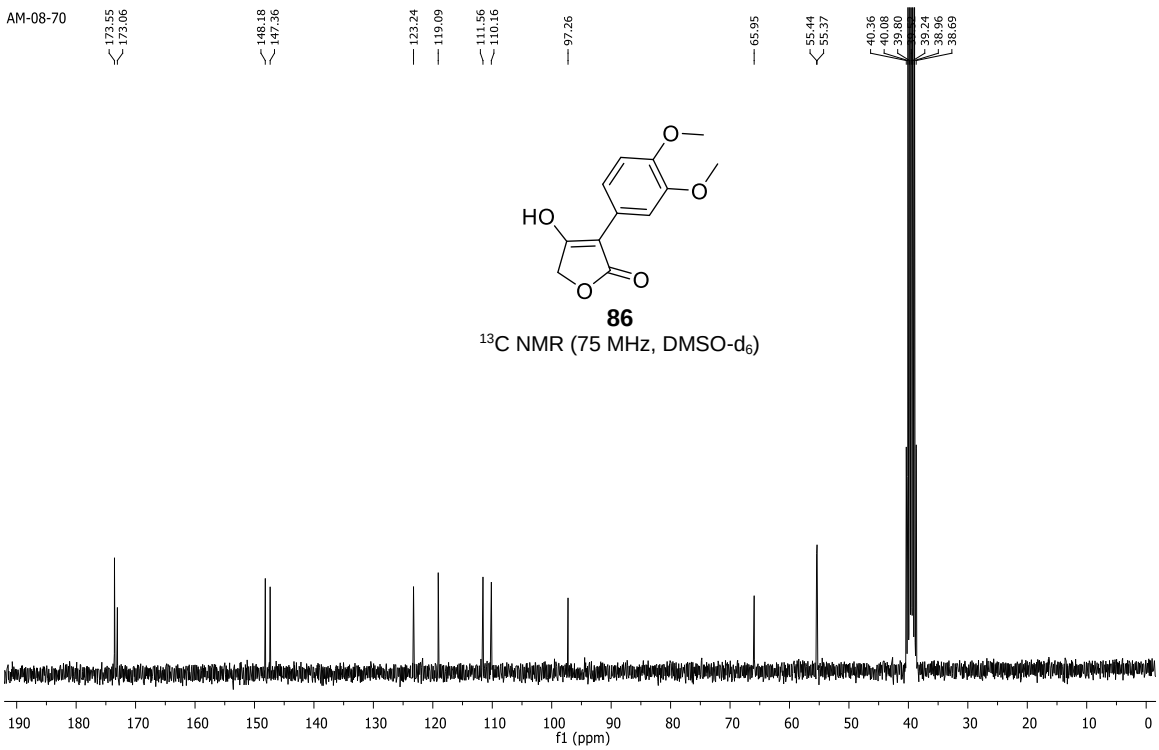
85

^{13}C NMR (75 MHz, DMSO-d_6)



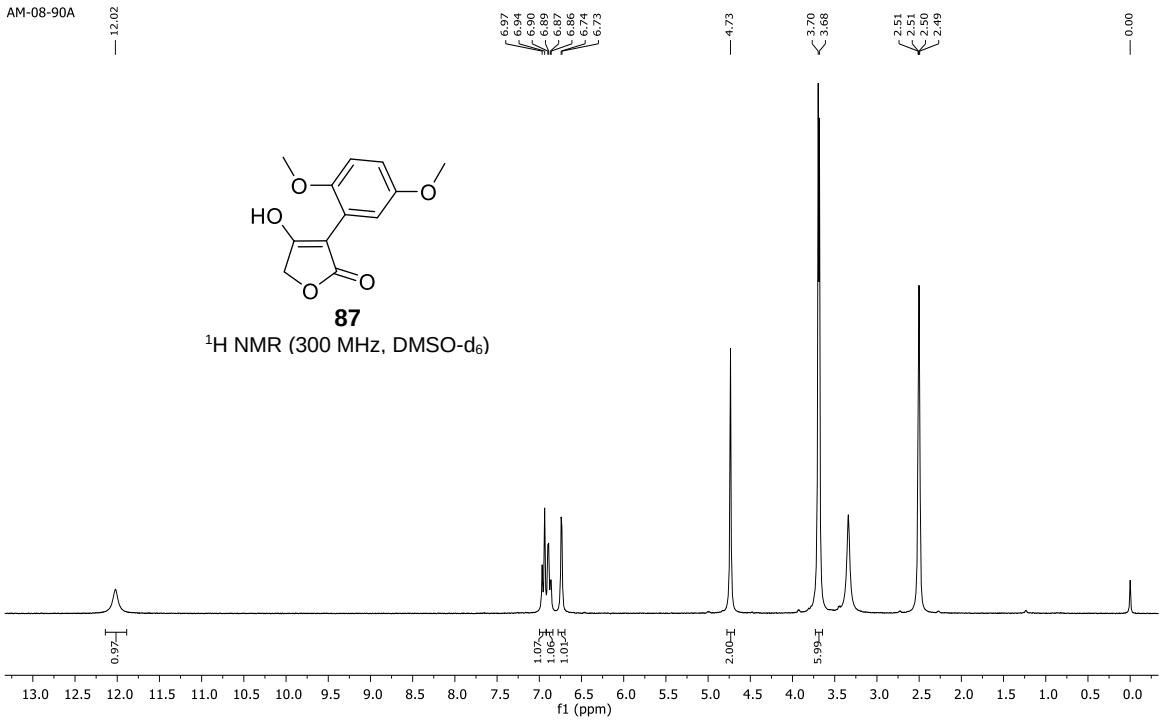
86

^{1}H NMR (300 MHz, DMSO-d_6)



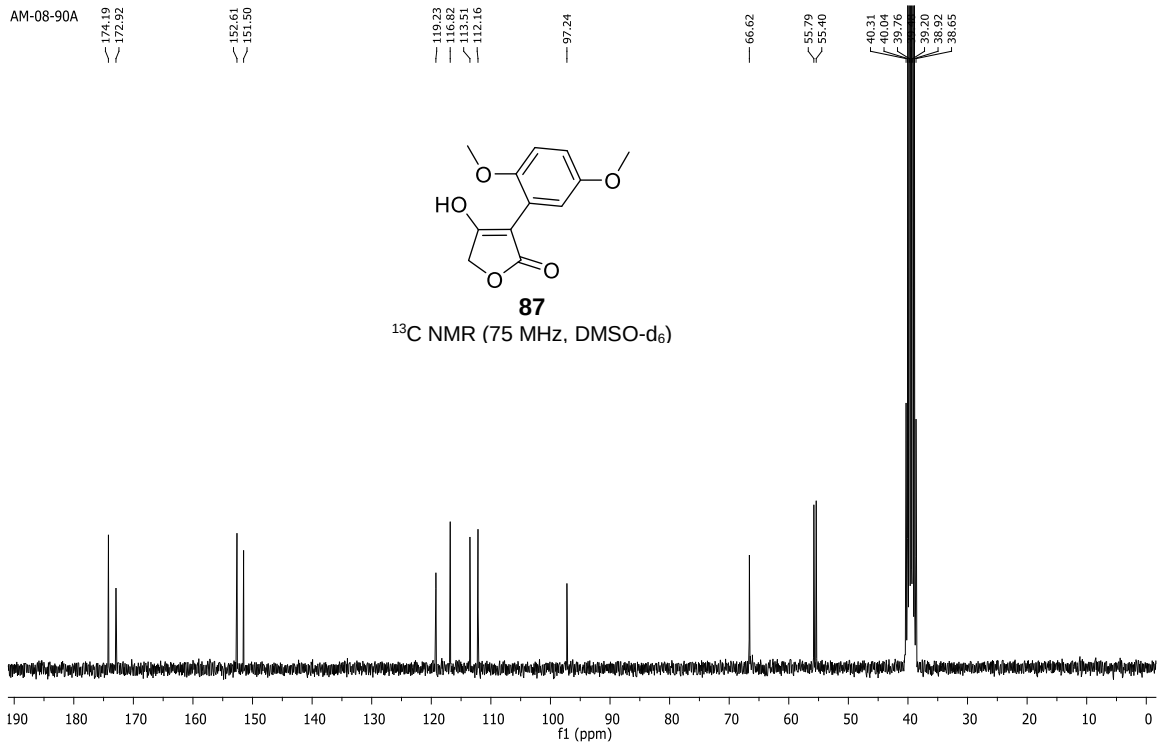
86

^{13}C NMR (75 MHz, DMSO-d_6)



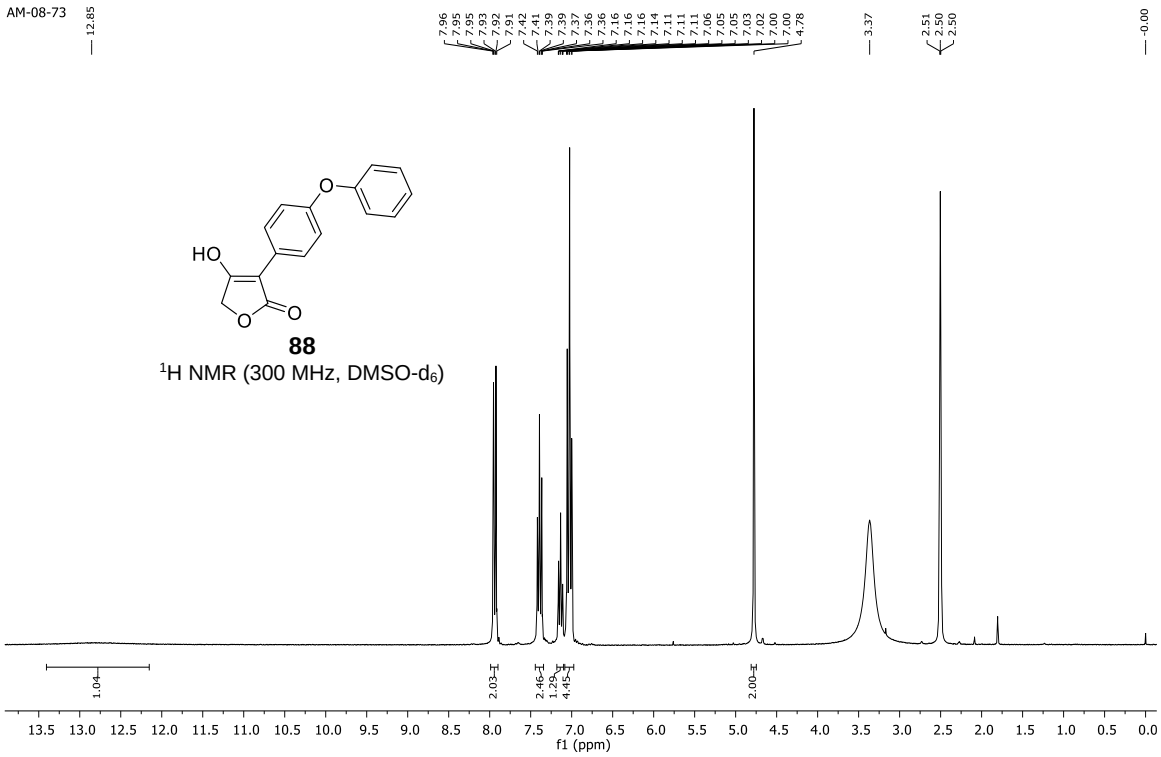
87

^{1}H NMR (300 MHz, DMSO-d_6)



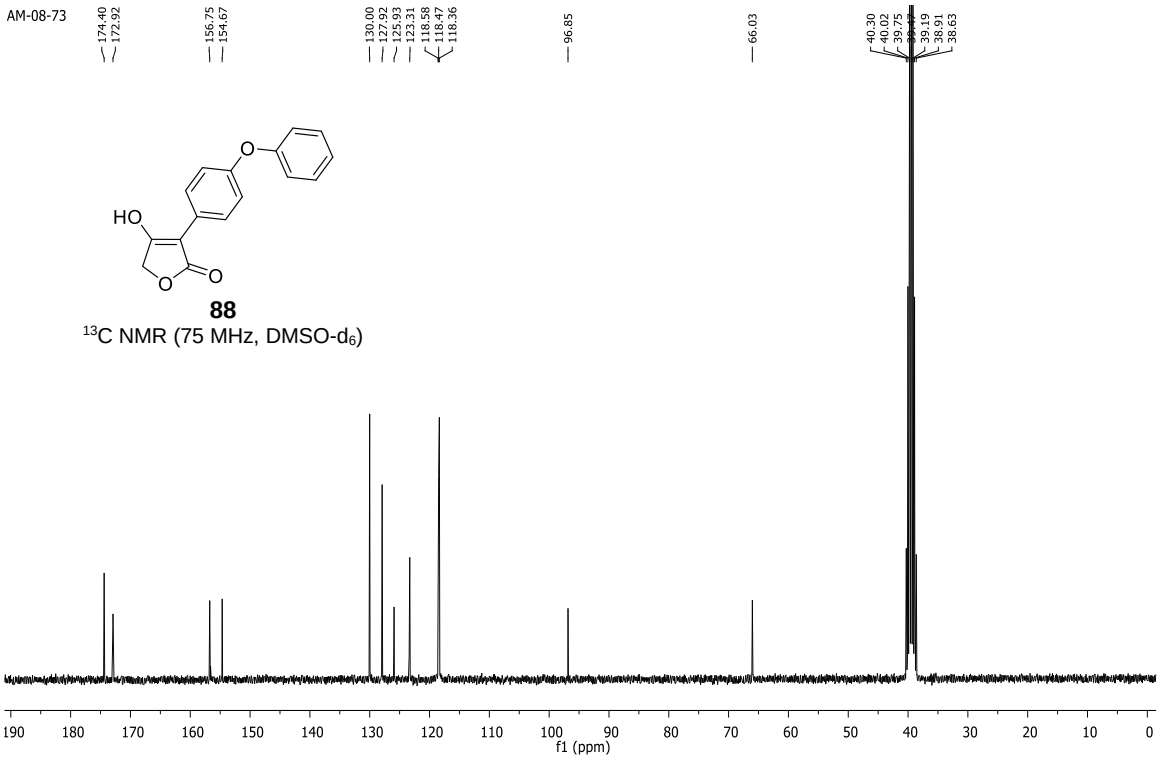
87

^{13}C NMR (75 MHz, DMSO-d_6)



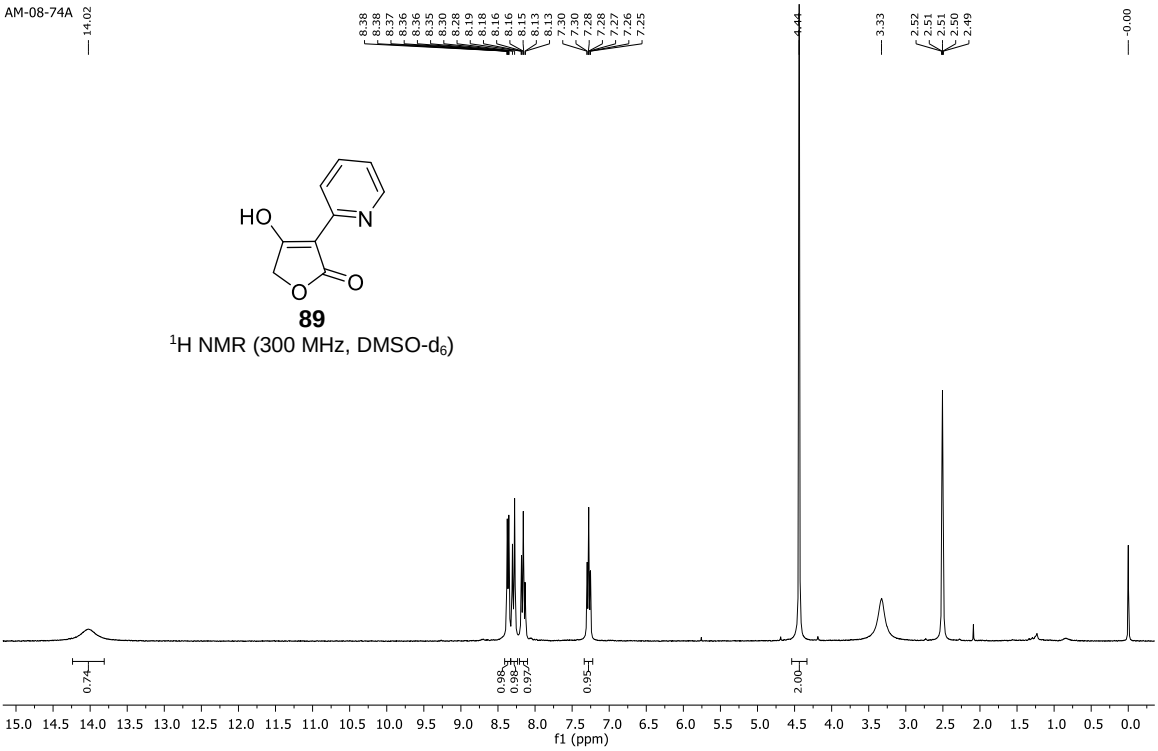
88

^{1}H NMR (300 MHz, DMSO-d_6)



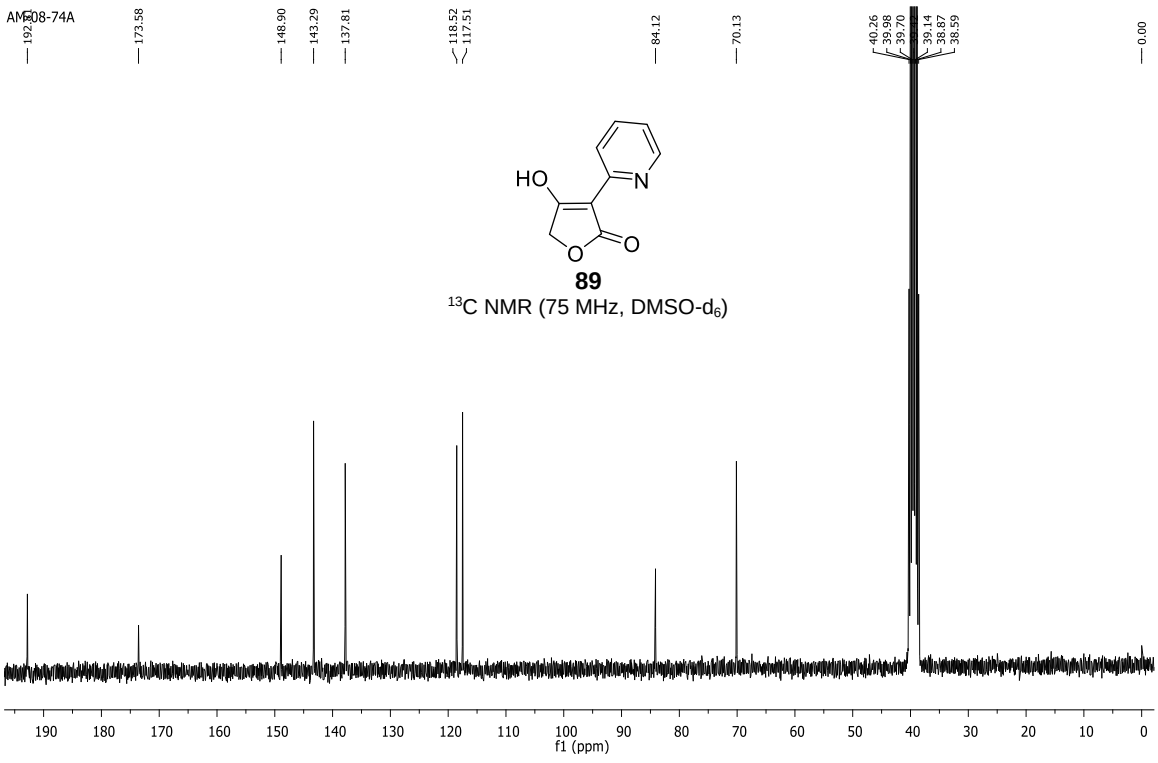
88

^{13}C NMR (75 MHz, DMSO-d_6)



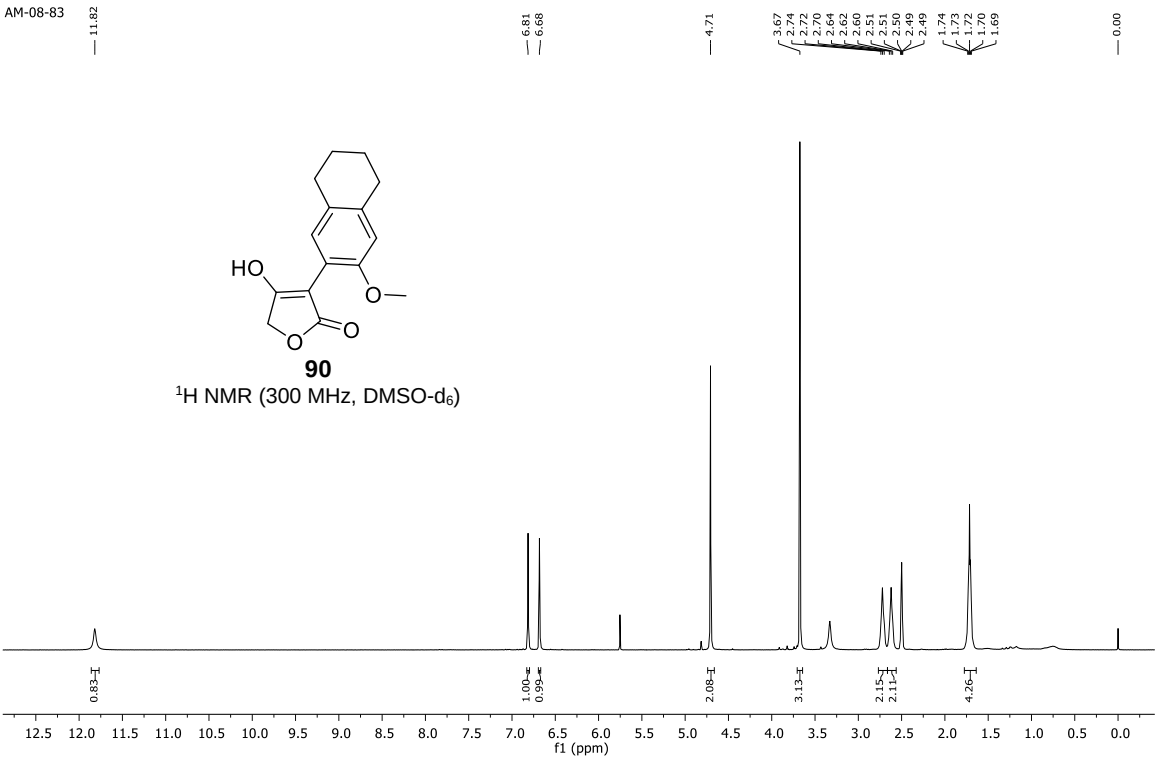
89

^{1}H NMR (300 MHz, DMSO-d_6)



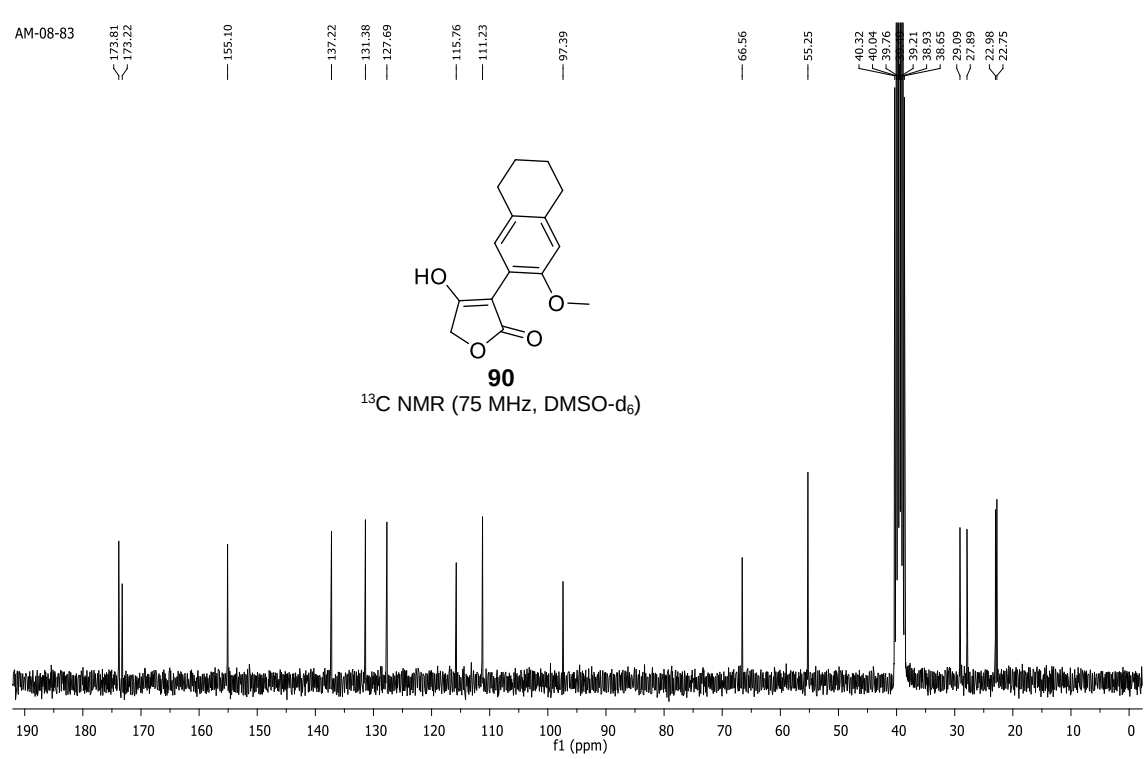
89

^{13}C NMR (75 MHz, DMSO-d_6)



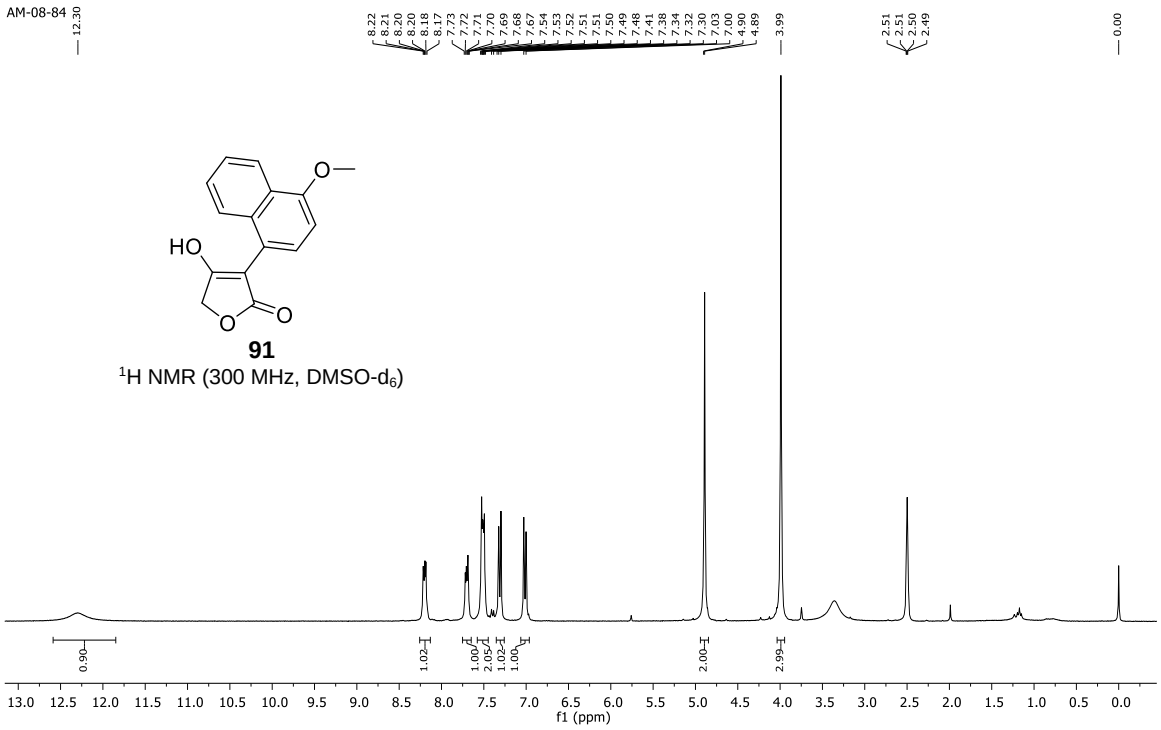
90

^{1}H NMR (300 MHz, DMSO-d_6)



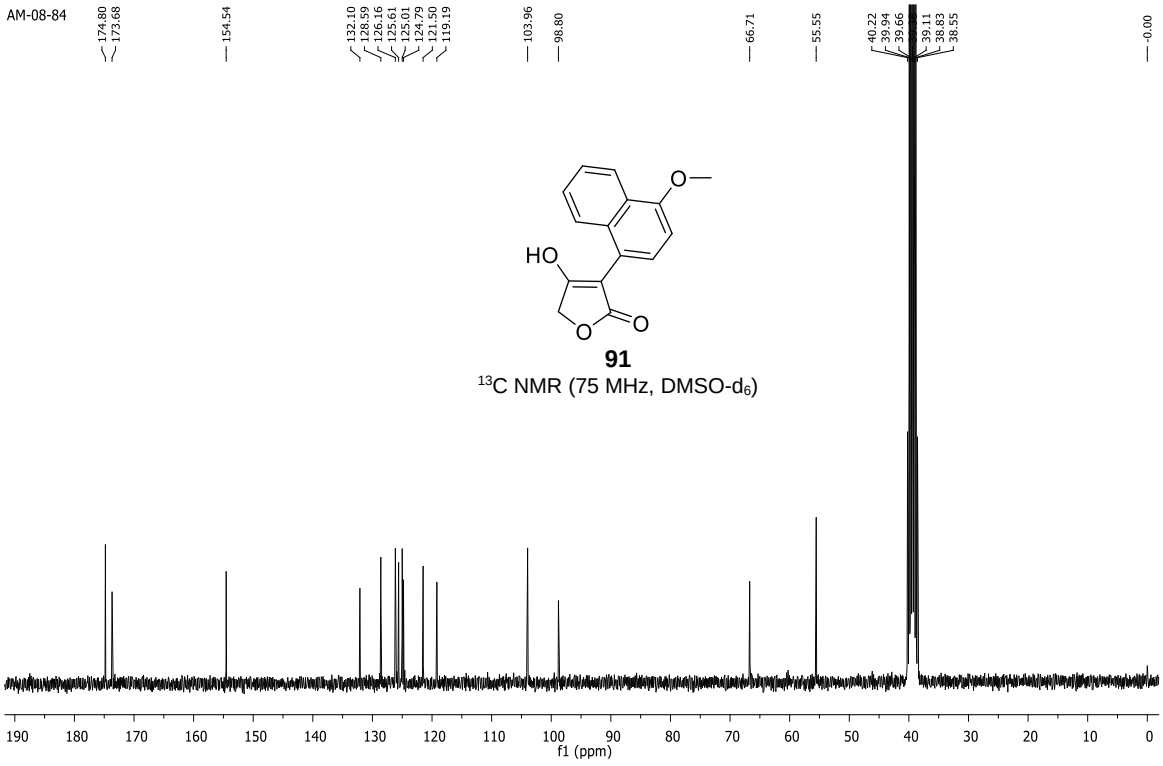
90

^{13}C NMR (75 MHz, DMSO-d_6)



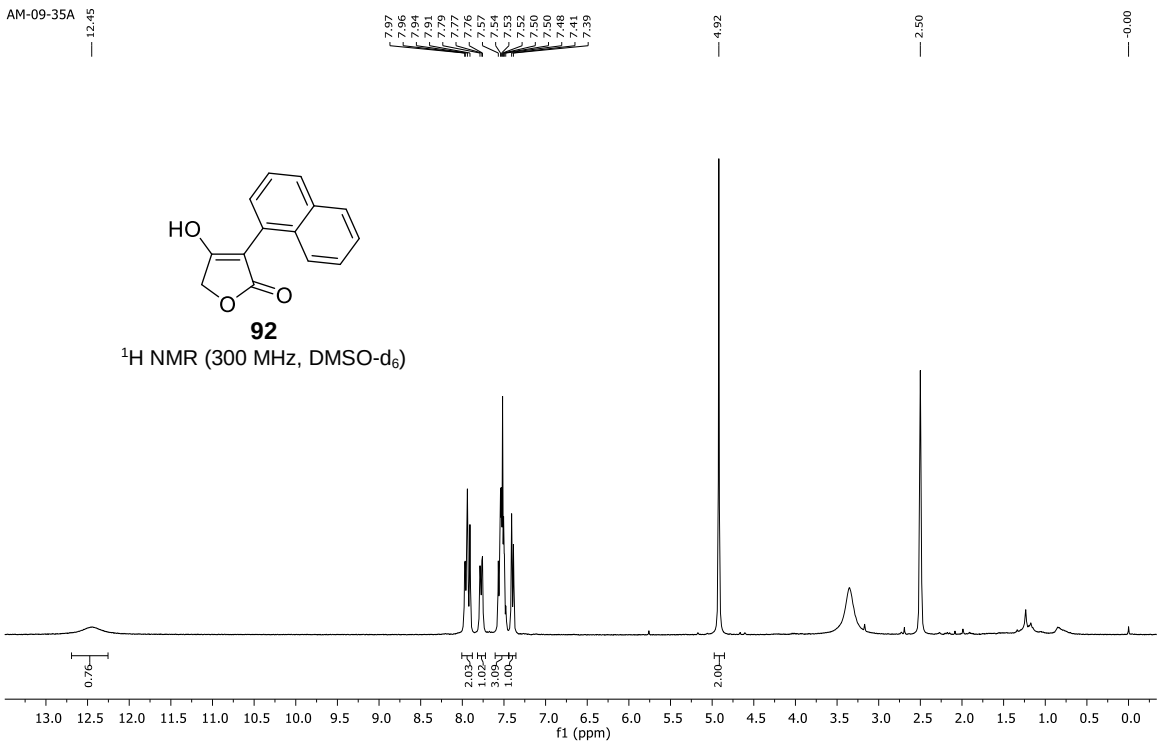
91

^{1}H NMR (300 MHz, DMSO-d_6)



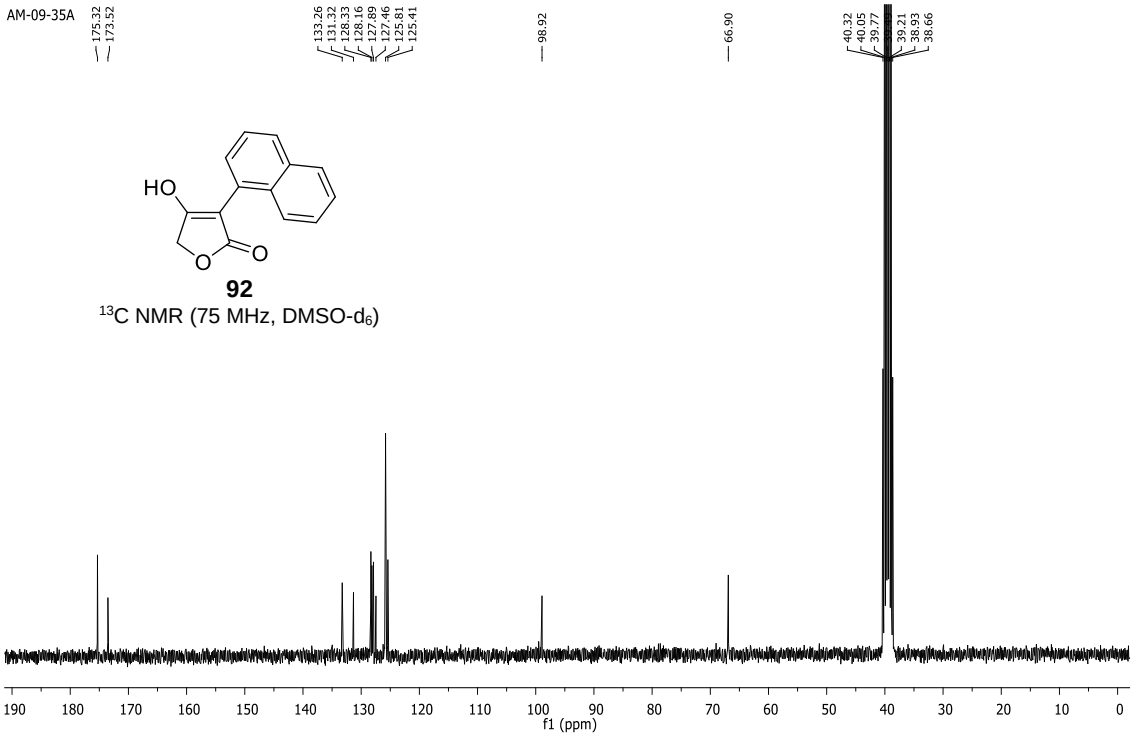
91

^{13}C NMR (75 MHz, DMSO-d_6)



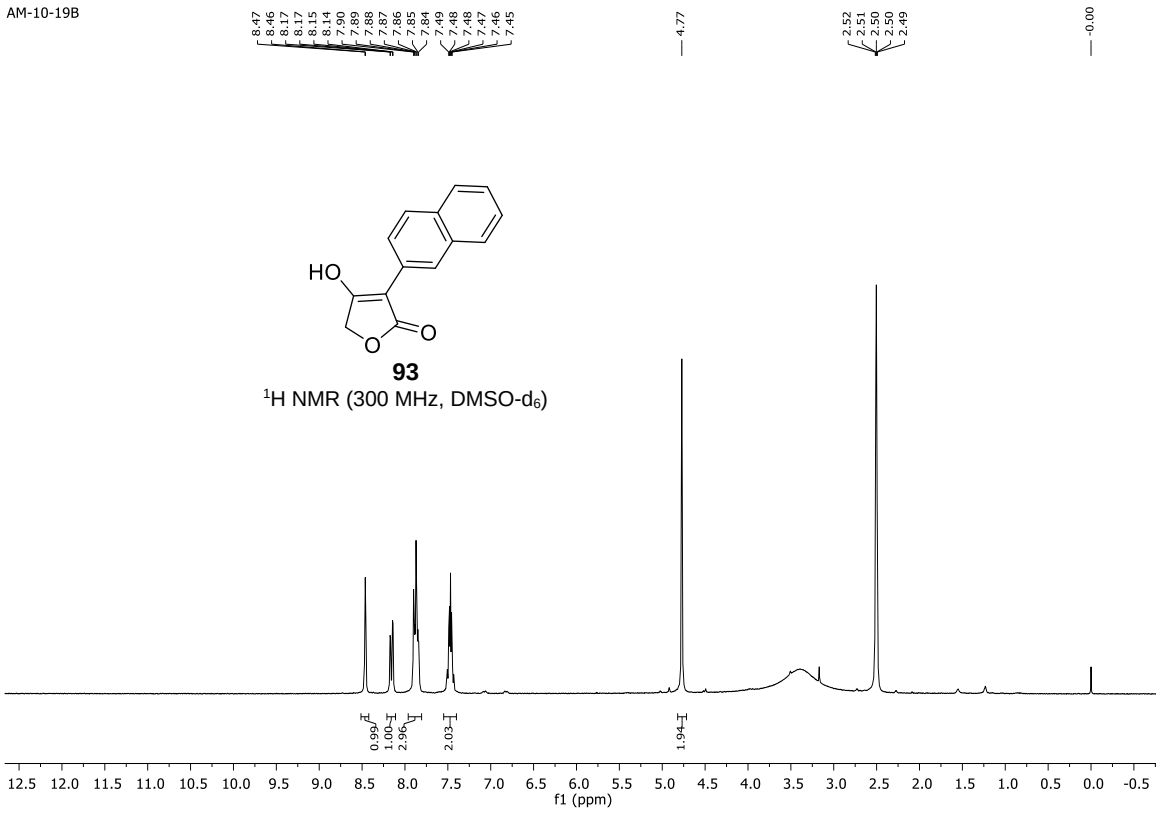
92

^{1}H NMR (300 MHz, DMSO-d_6)



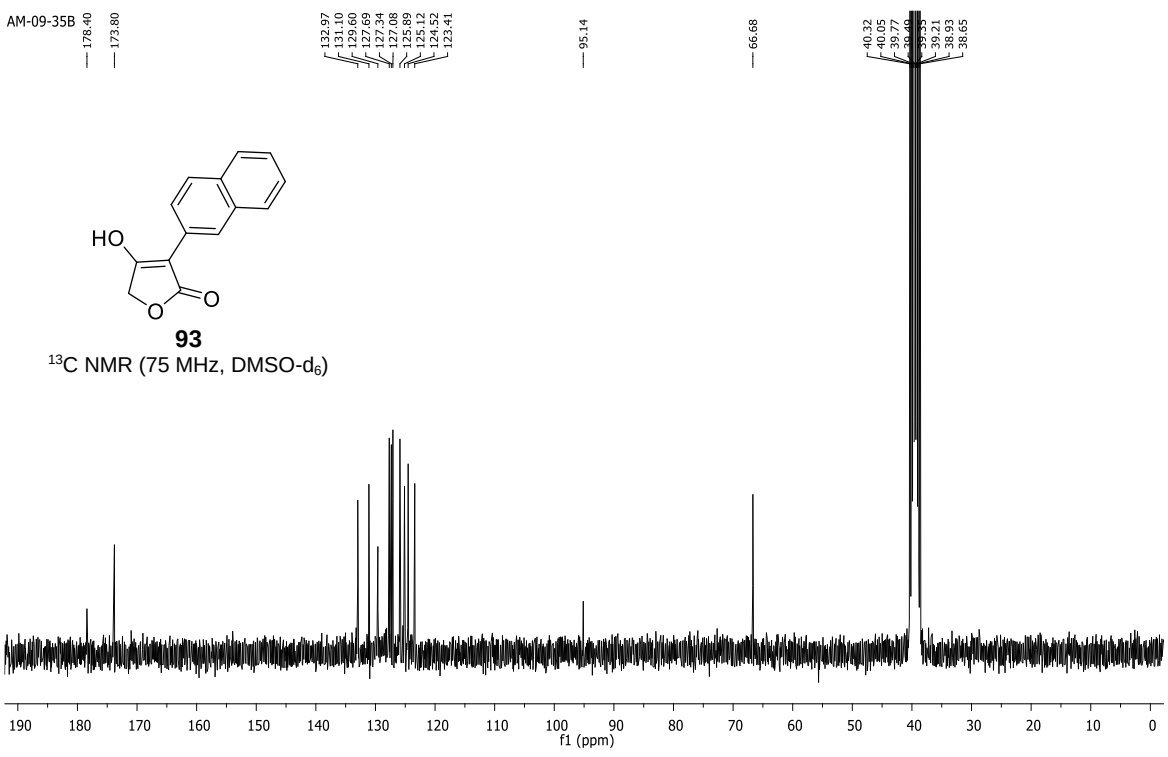
92

^{13}C NMR (75 MHz, DMSO-d_6)



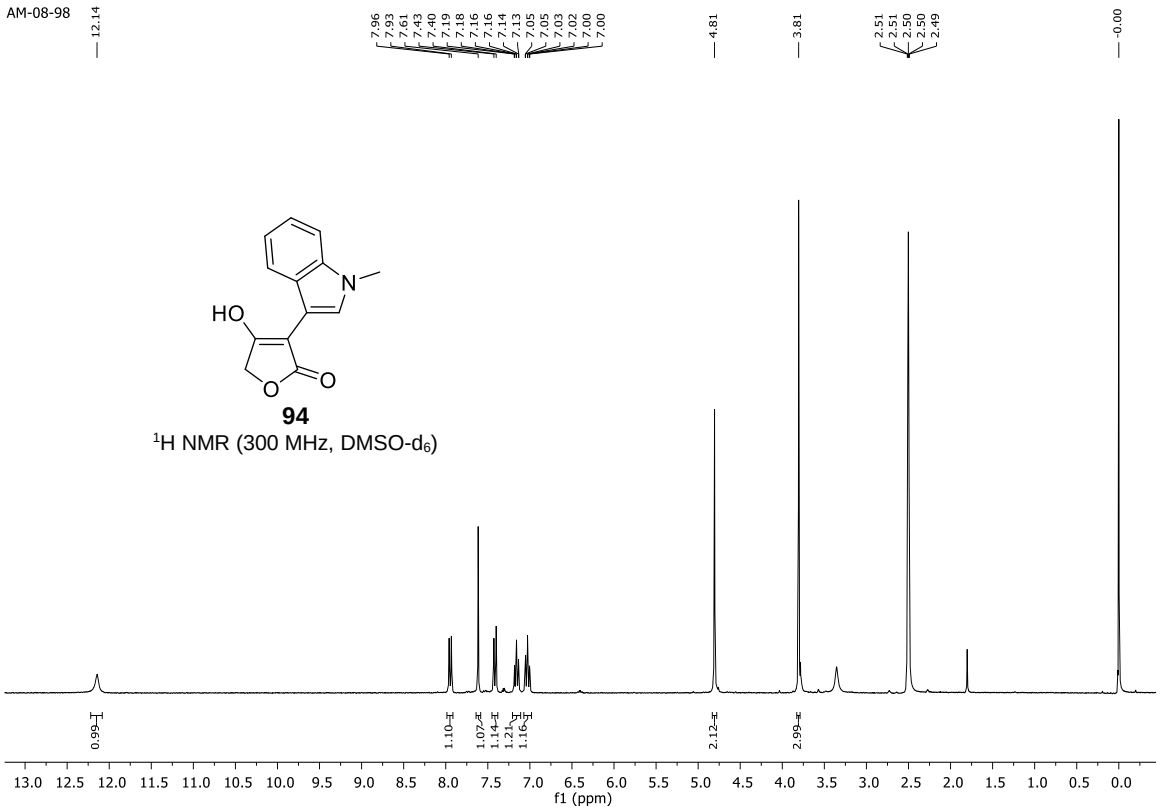
93

^{1}H NMR (300 MHz, DMSO-d_6)



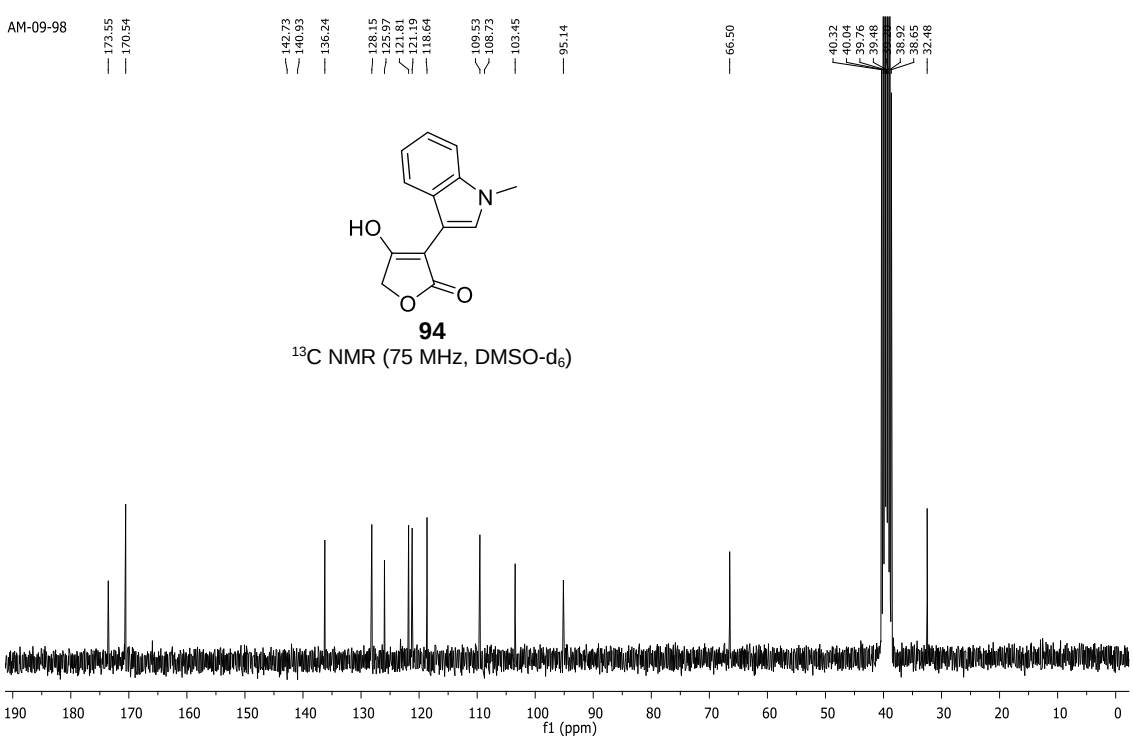
93

^{13}C NMR (75 MHz, DMSO-d_6)



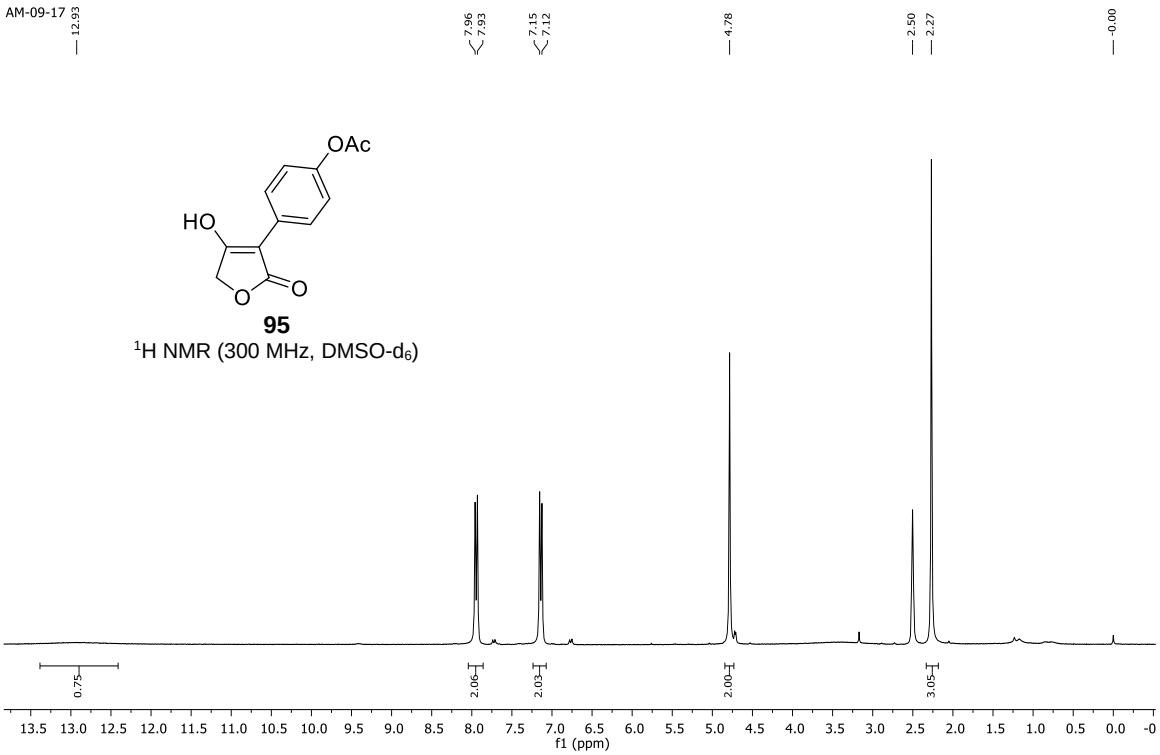
94

^{1}H NMR (300 MHz, DMSO-d_6)



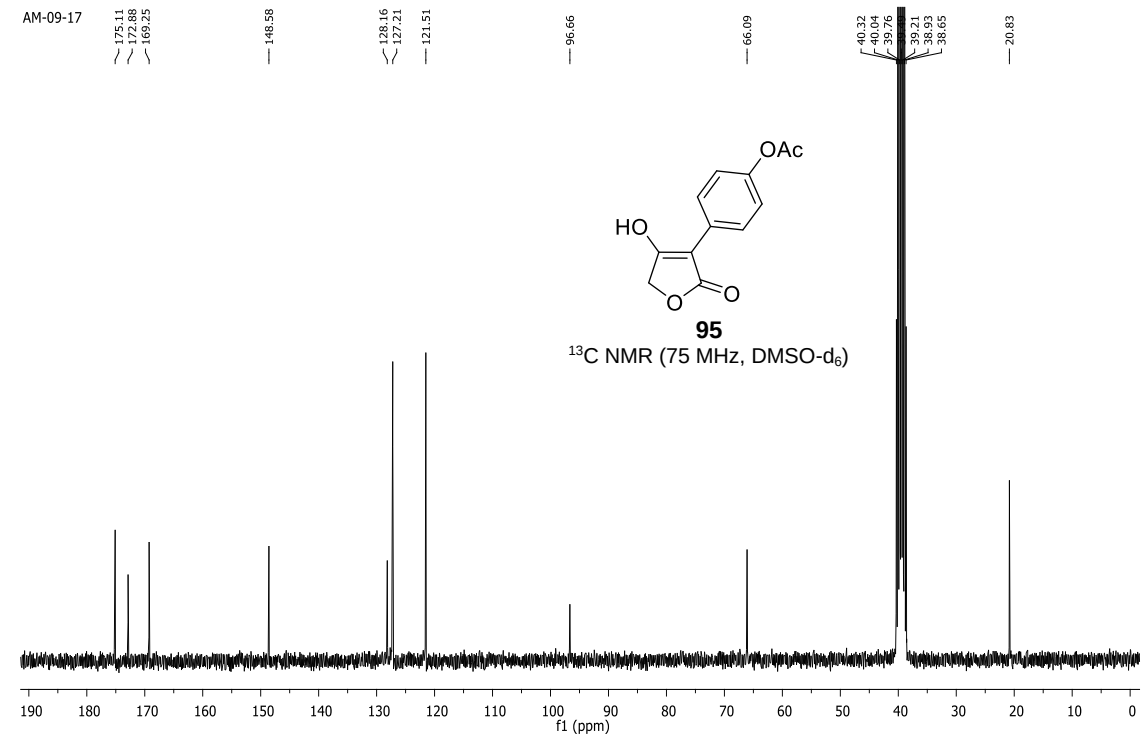
94

^{13}C NMR (75 MHz, DMSO-d_6)



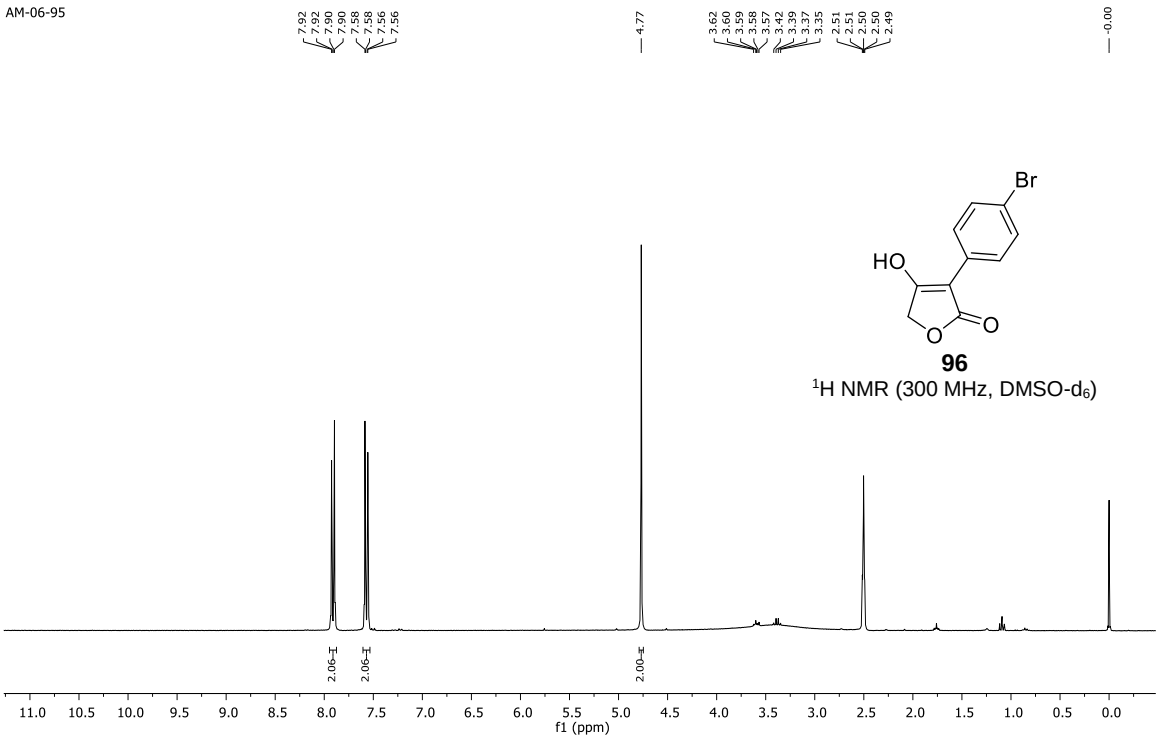
95

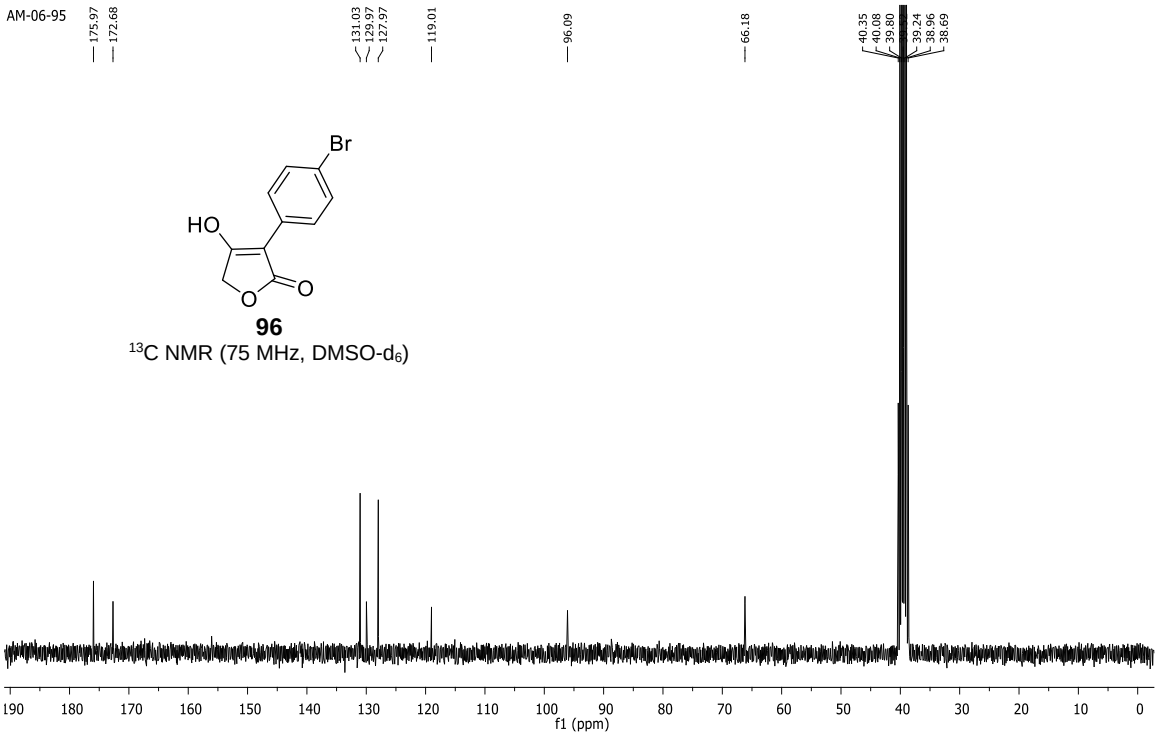
^{1}H NMR (300 MHz, DMSO-d_6)

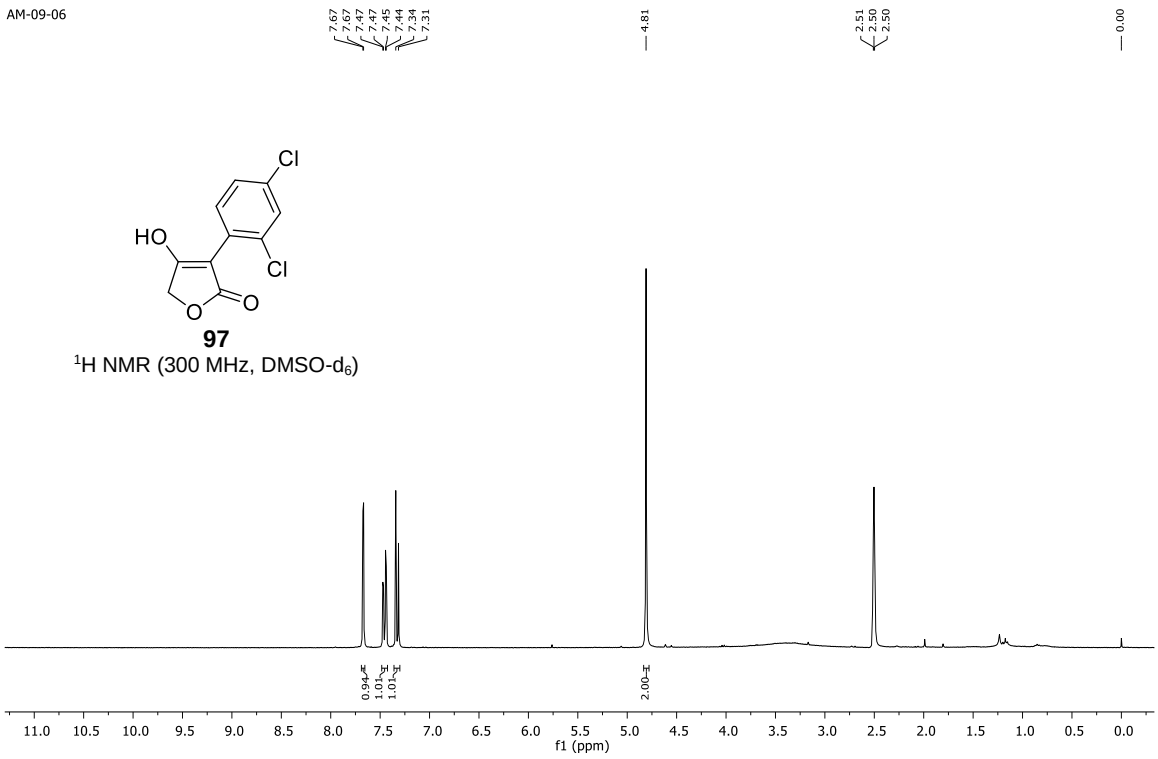


95

^{13}C NMR (75 MHz, DMSO-d_6)

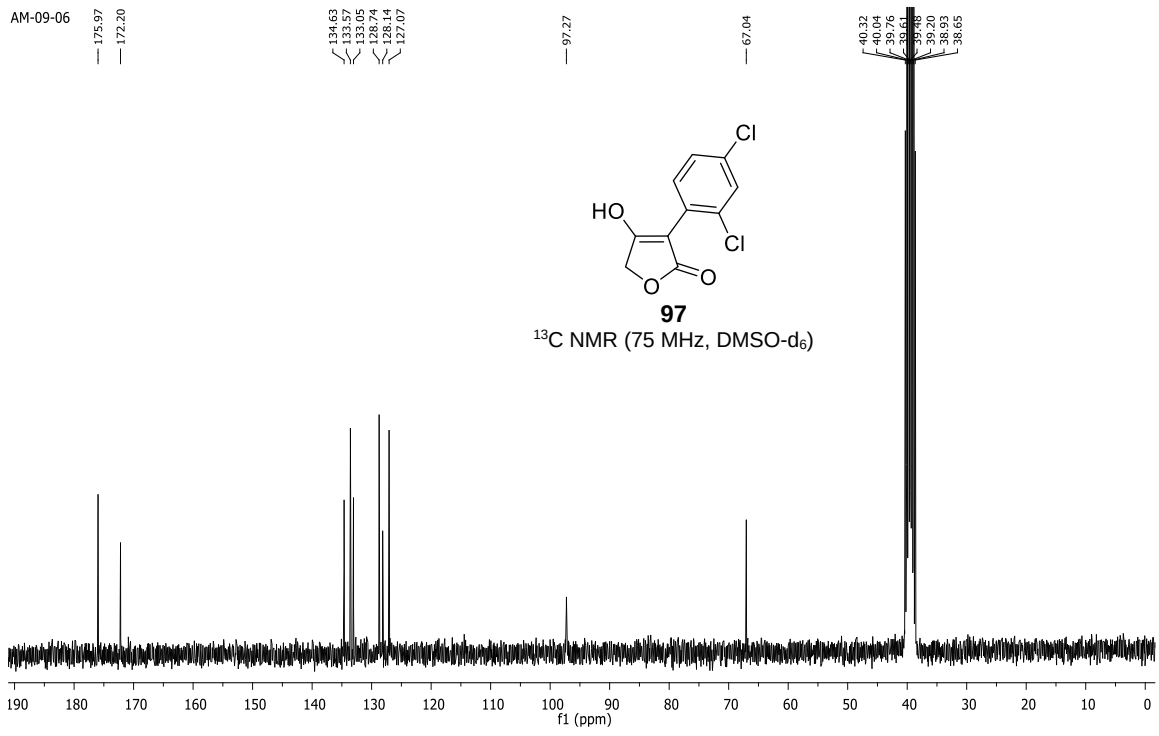

AM-06-95
7.92
7.92
7.90
7.90
7.58
7.58
7.56
7.56
4.77
3.62
3.60
3.59
3.58
3.57
3.42
3.39
3.37
3.35
2.51
2.51
2.50
2.50
2.49
-0.00
Br
HO
O
O
96
1H NMR (300 MHz, DMSO-d6)
2.06
2.06
2.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AM-06-95
175.97
172.68
131.03
129.97
127.97
119.01
96.09
66.18
40.35
40.08
39.80
39.24
38.96
38.69
Br
HO
O
O
96
13C NMR (75 MHz, DMSO-d6)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



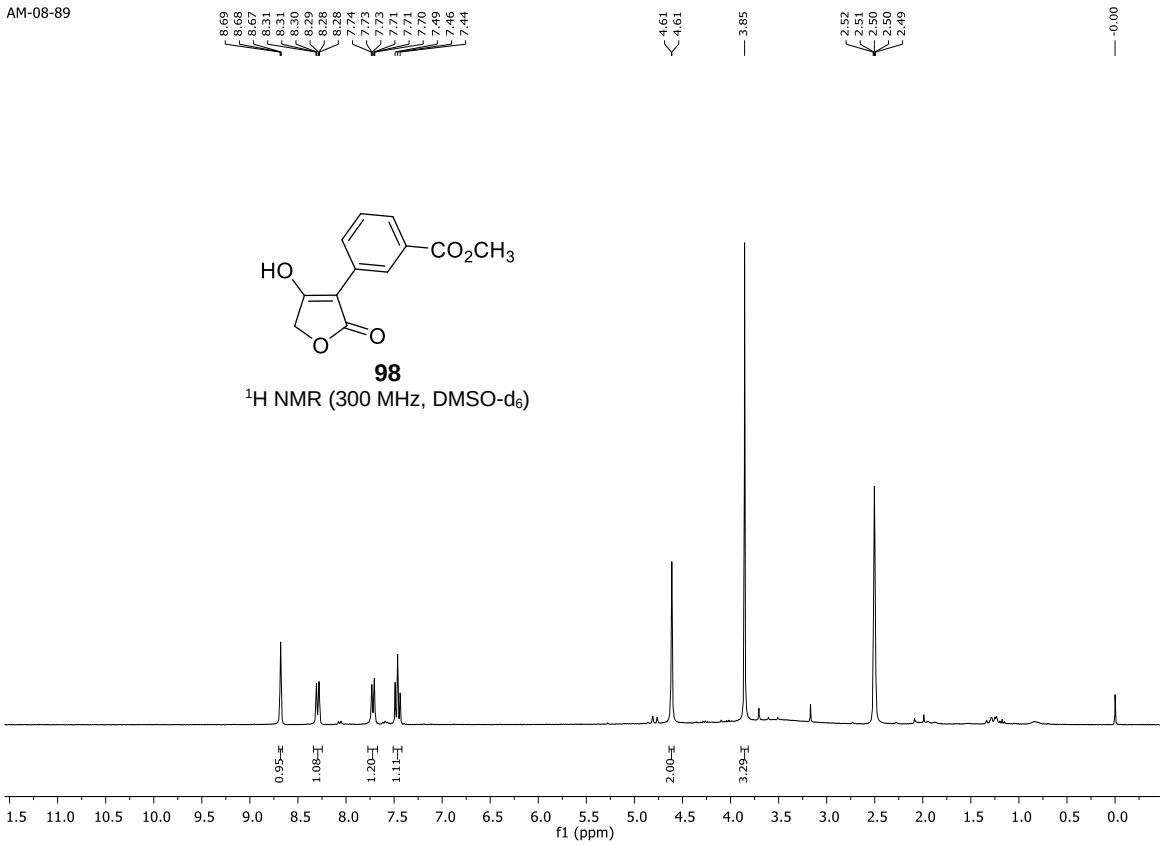
97

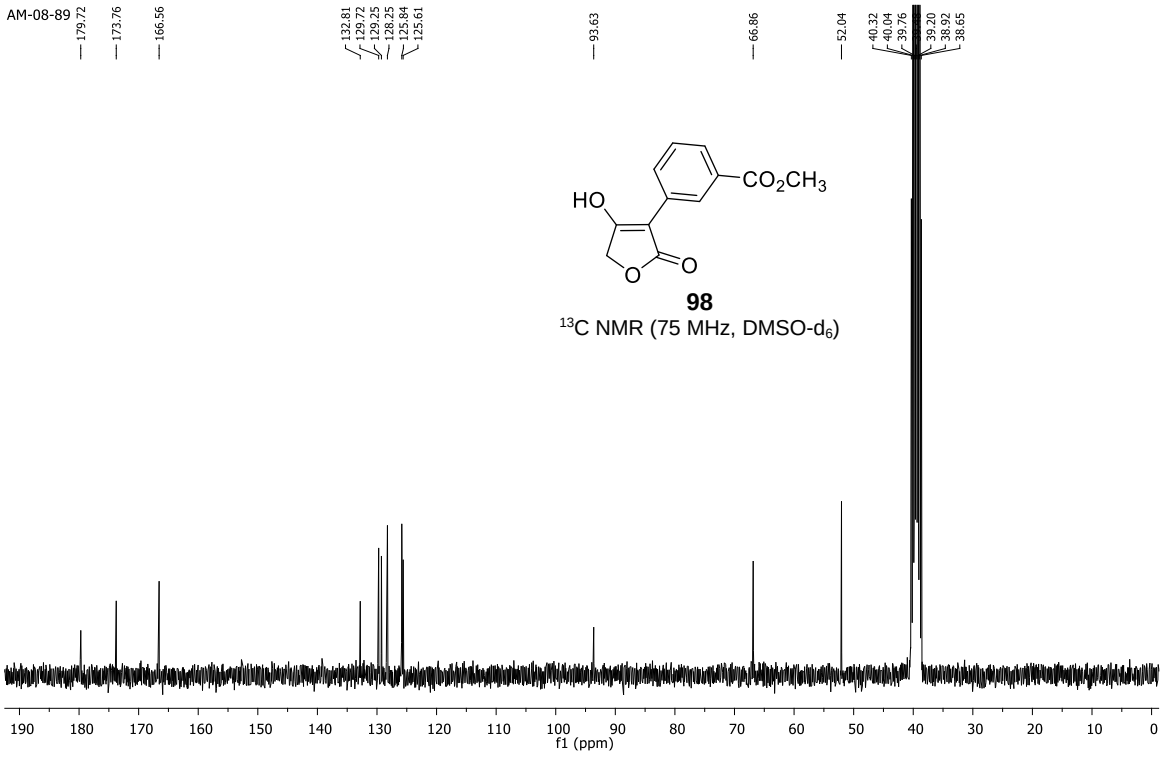
^{1}H NMR (300 MHz, DMSO-d_6)

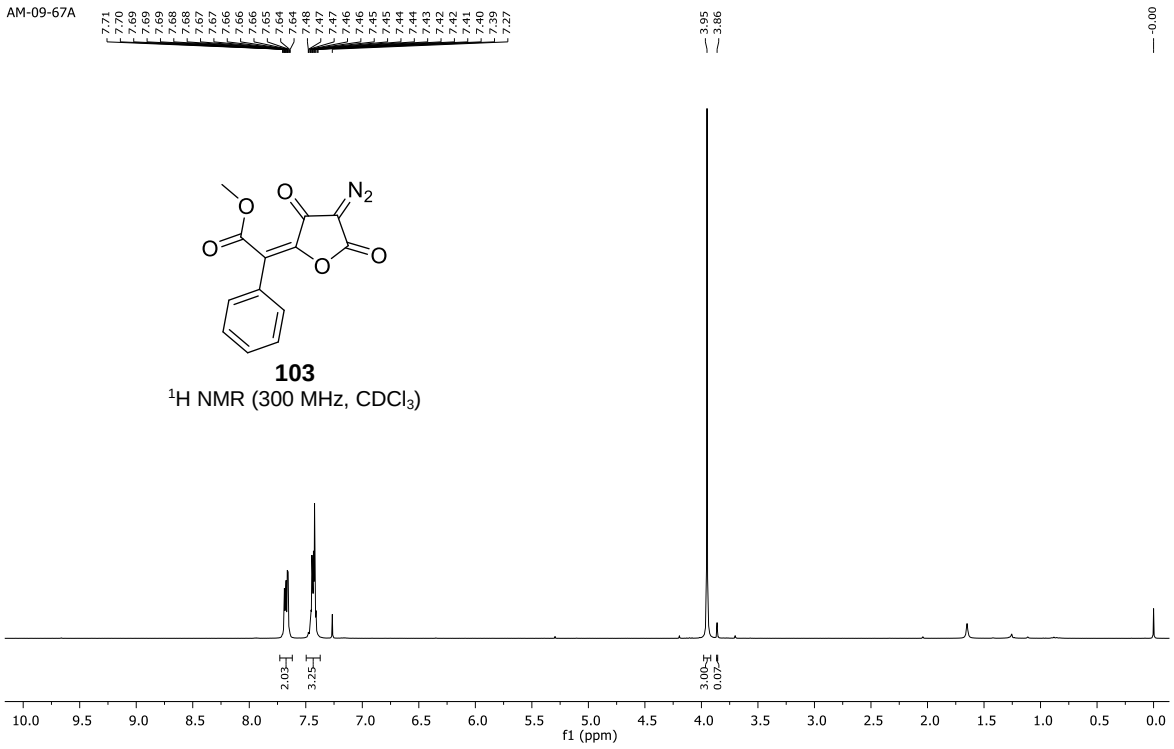


97

^{13}C NMR (75 MHz, DMSO-d_6)

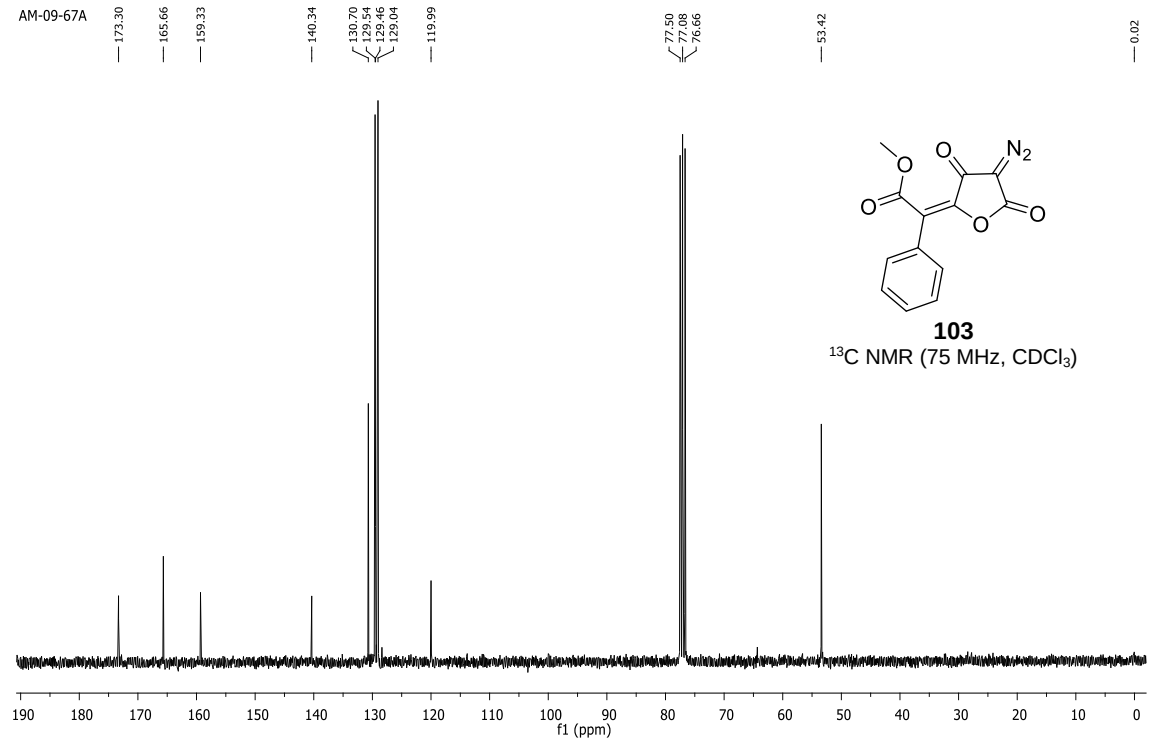

AM-08-89
8.69
8.68
8.67
8.31
8.31
8.30
8.29
8.28
8.28
7.74
7.73
7.73
7.71
7.71
7.70
7.49
7.46
7.44
4.61
4.61
3.85
2.52
2.51
2.50
2.50
2.49
-0.00
HO
CO2CH3
O
O
98
1H NMR (300 MHz, DMSO-d6)
0.95
1.08
1.20
1.11
2.00
3.29
f1 (ppm)


AM-08-89
179.72
173.76
166.56
132.81
129.72
129.25
128.25
125.84
125.61
93.63
66.86
52.04
40.32
40.04
39.76
39.20
38.92
38.65
HO
CO2CH3
O
O
98
13C NMR (75 MHz, DMSO-d6)
f1 (ppm)



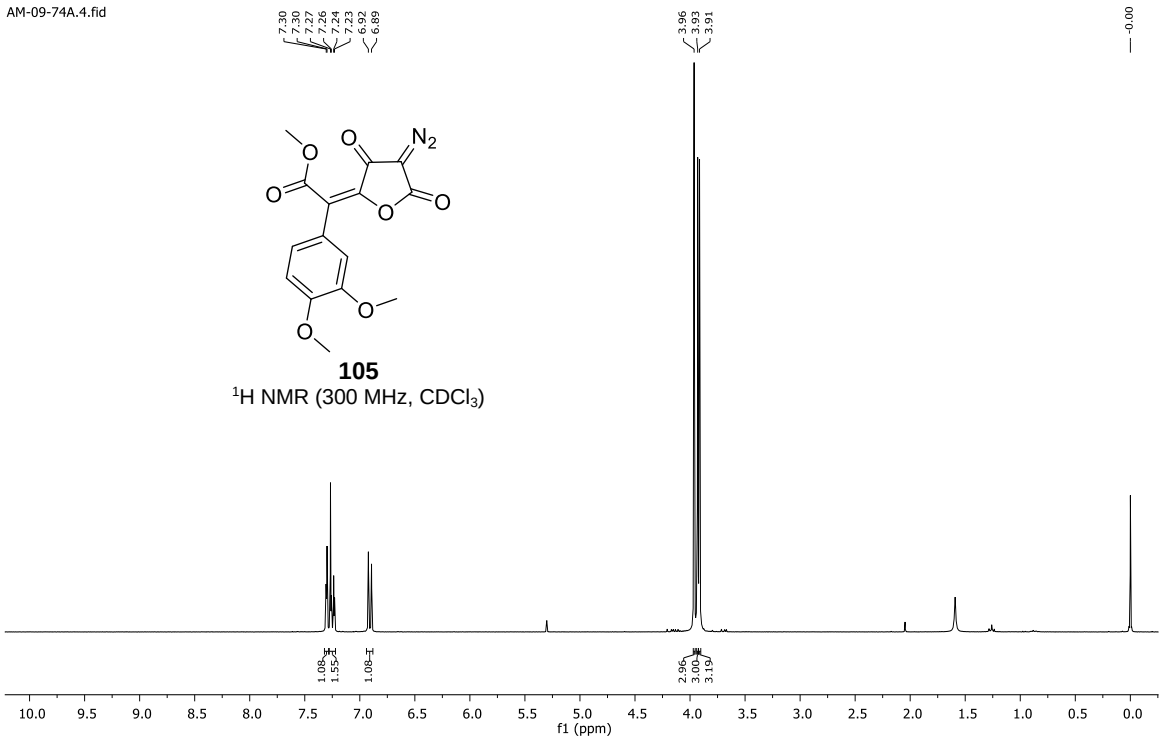
103

^{1}H NMR (300 MHz, $CDCl_3$)



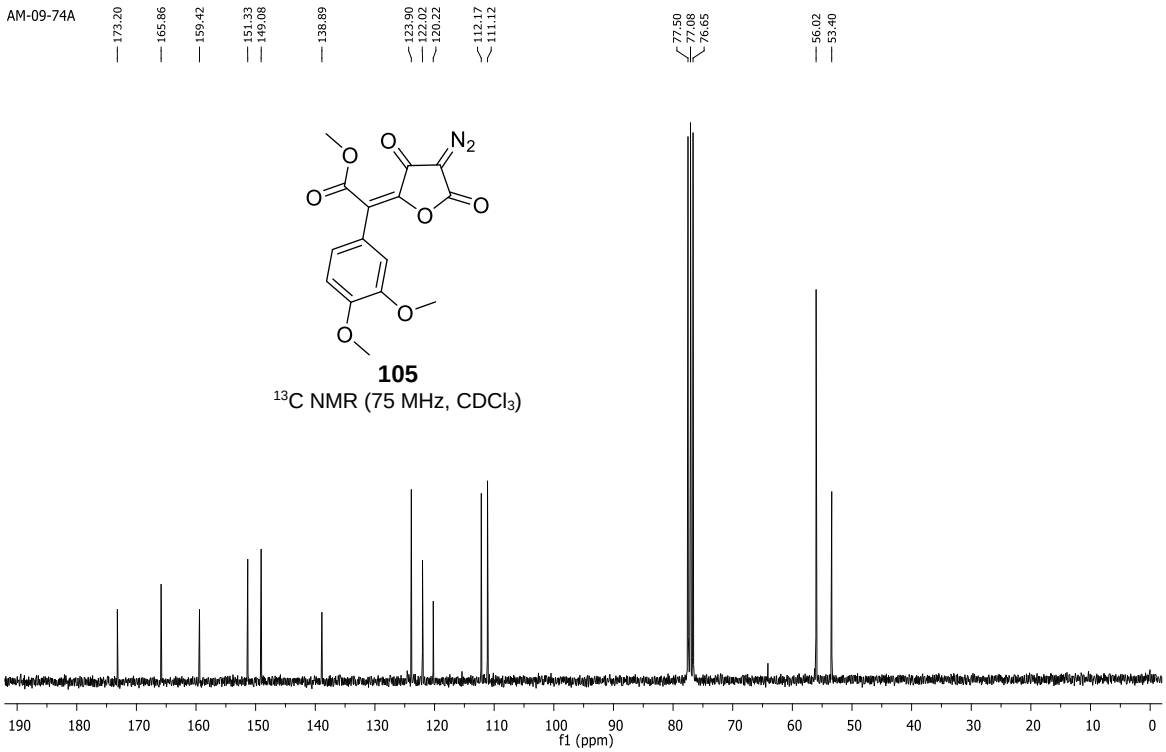
103

^{13}C NMR (75 MHz, $CDCl_3$)



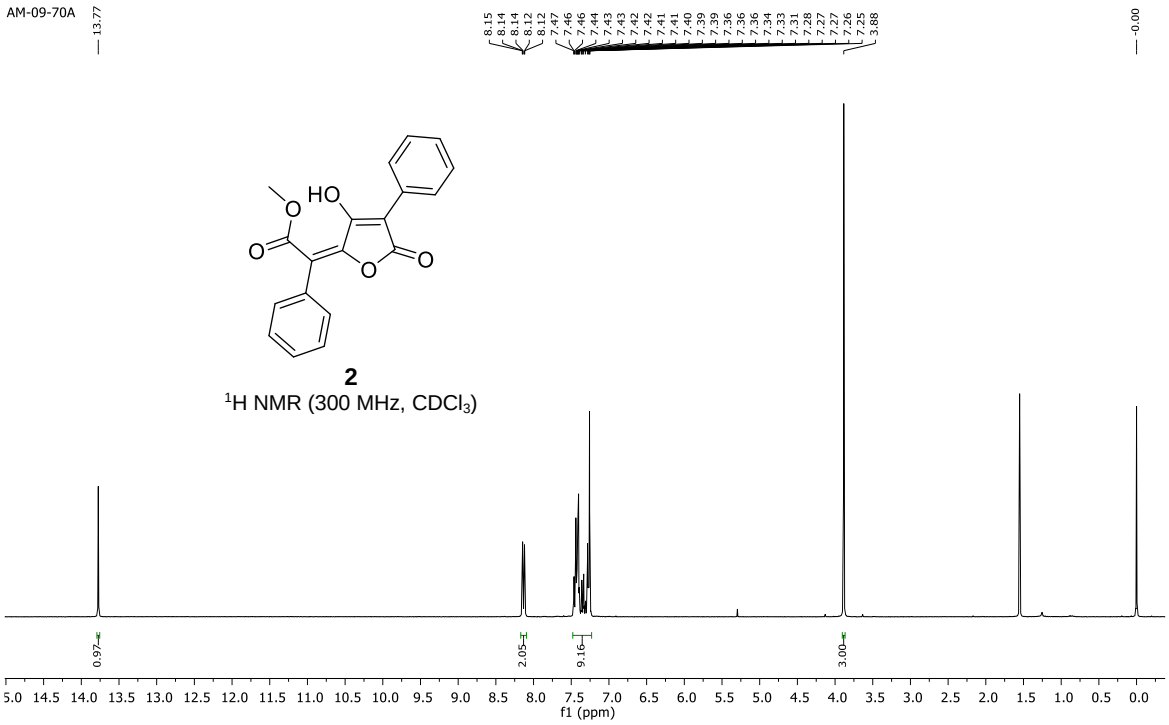
105

^{1}H NMR (300 MHz, $CDCl_3$)



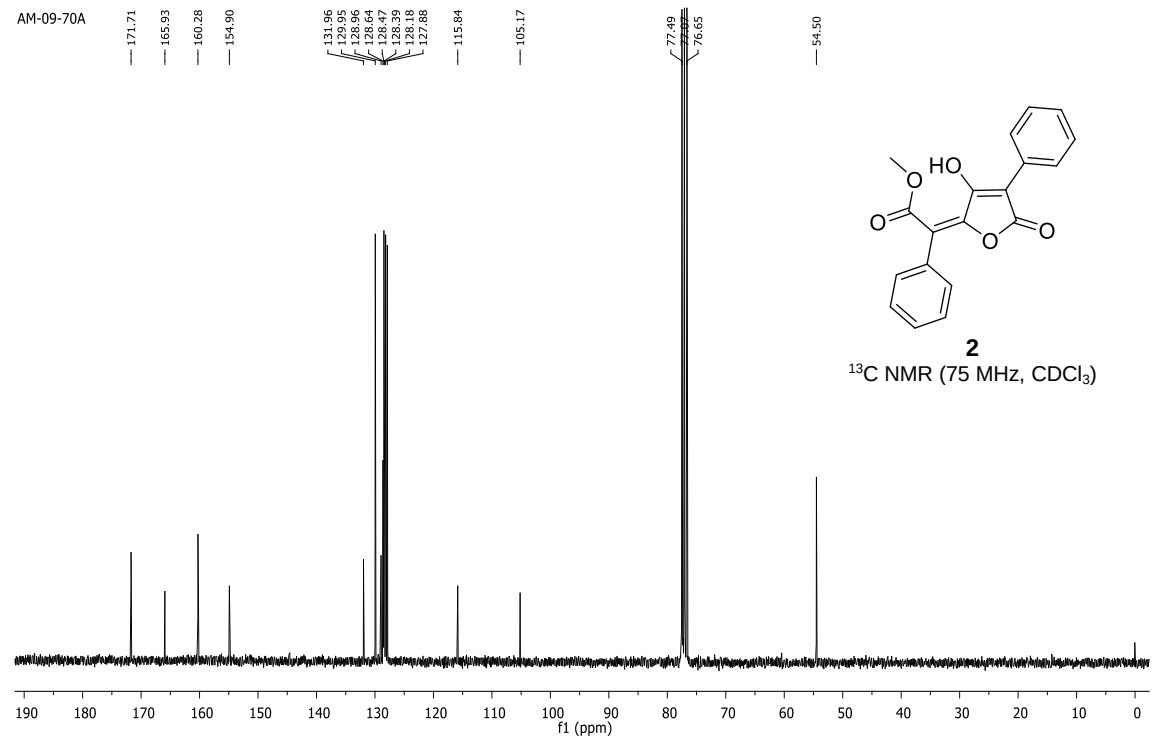
105

^{13}C NMR (75 MHz, $CDCl_3$)



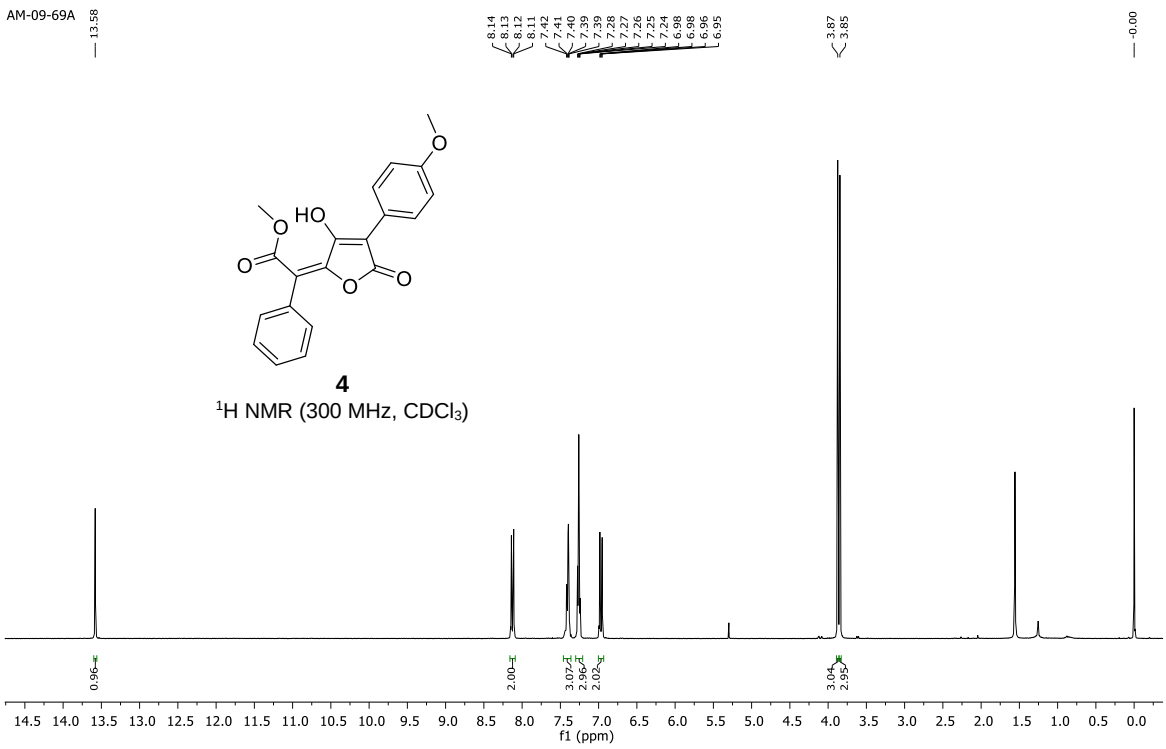
2

^{1}H NMR (300 MHz, $CDCl_3$)



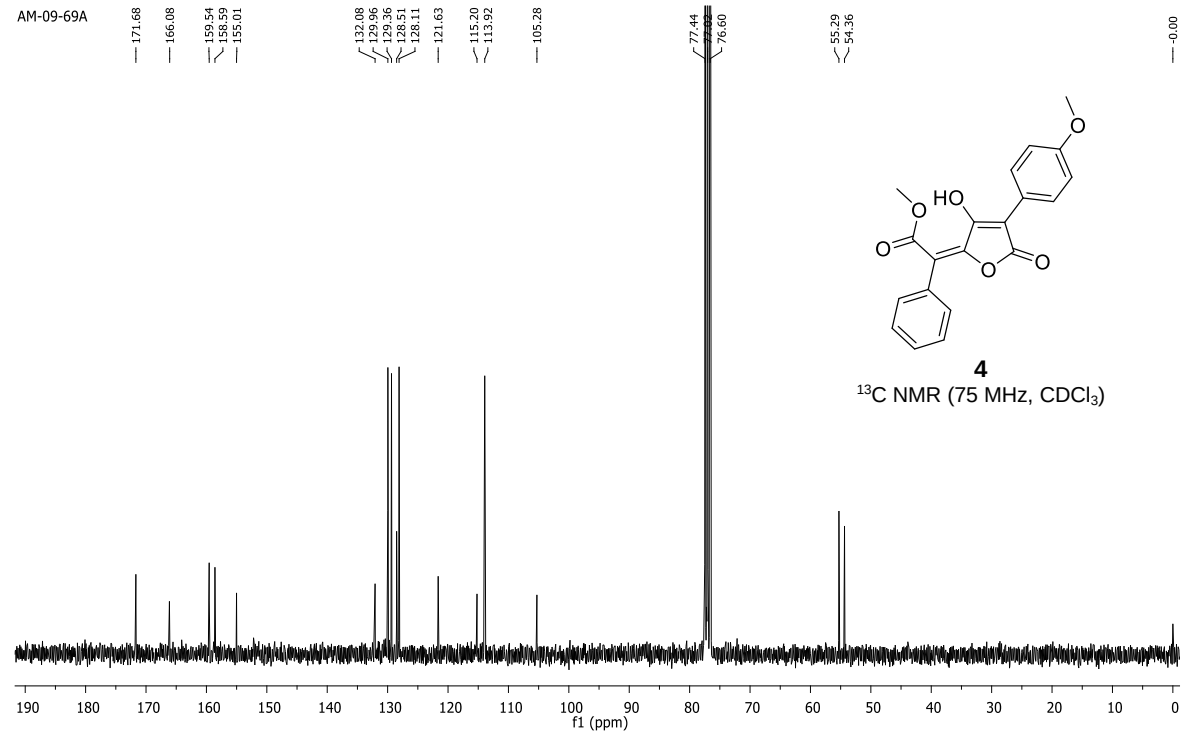
2

^{13}C NMR (75 MHz, $CDCl_3$)



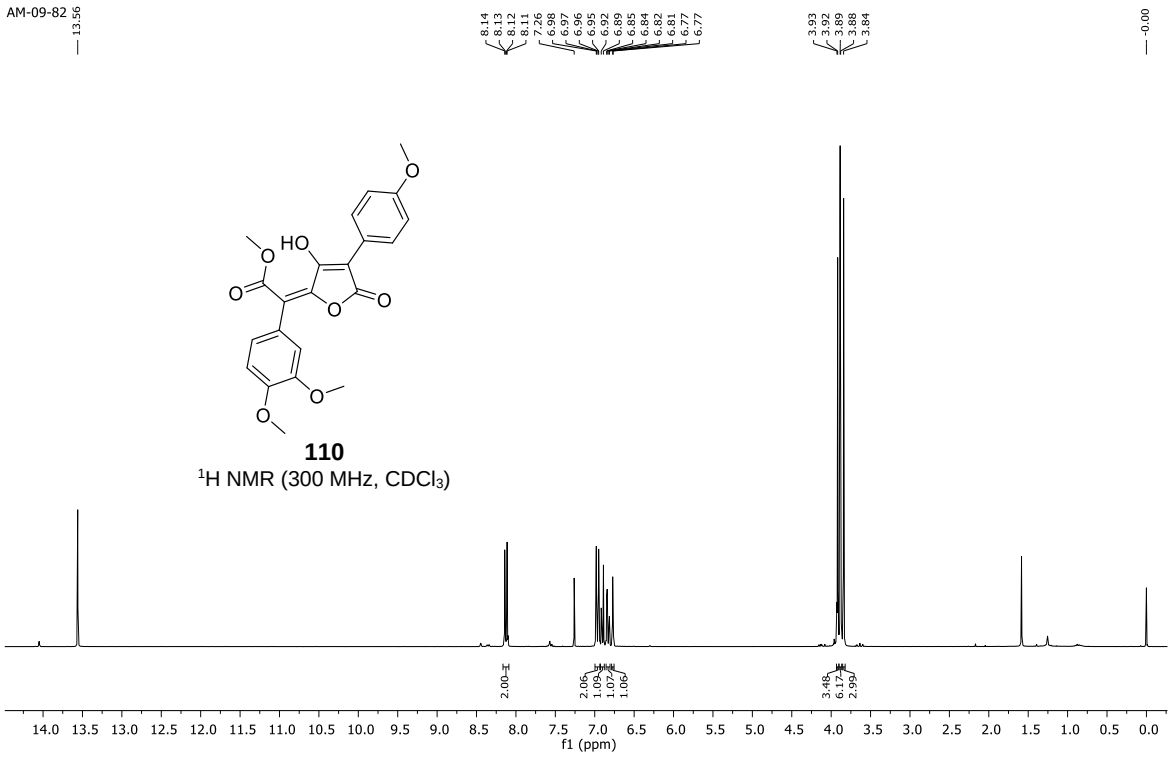
4

^{1}H NMR (300 MHz, $CDCl_3$)



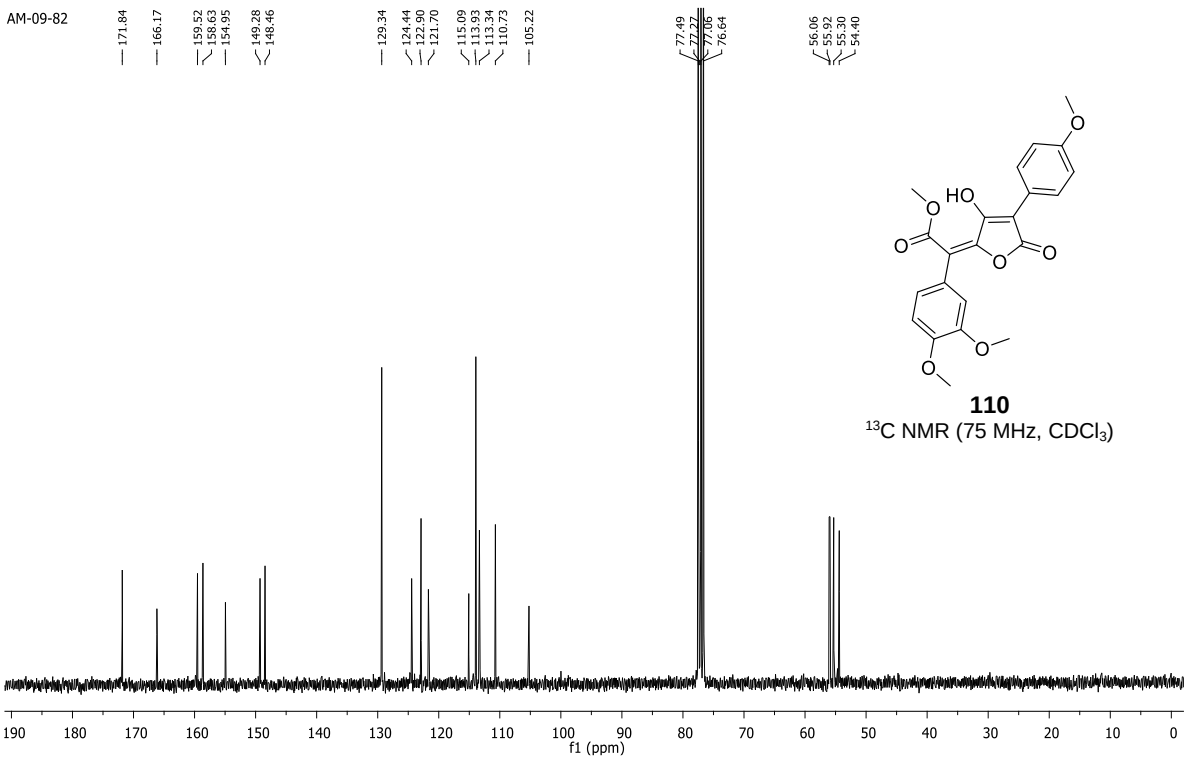
4

^{13}C NMR (75 MHz, $CDCl_3$)



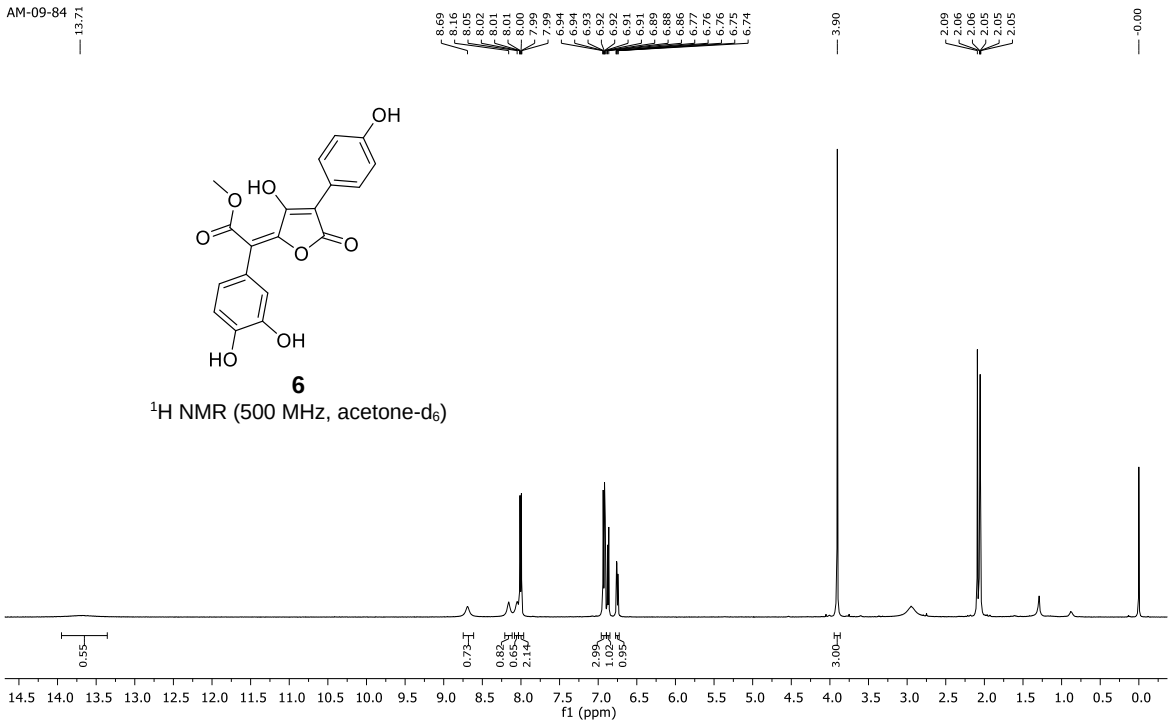
110

^{1}H NMR (300 MHz, $CDCl_3$)



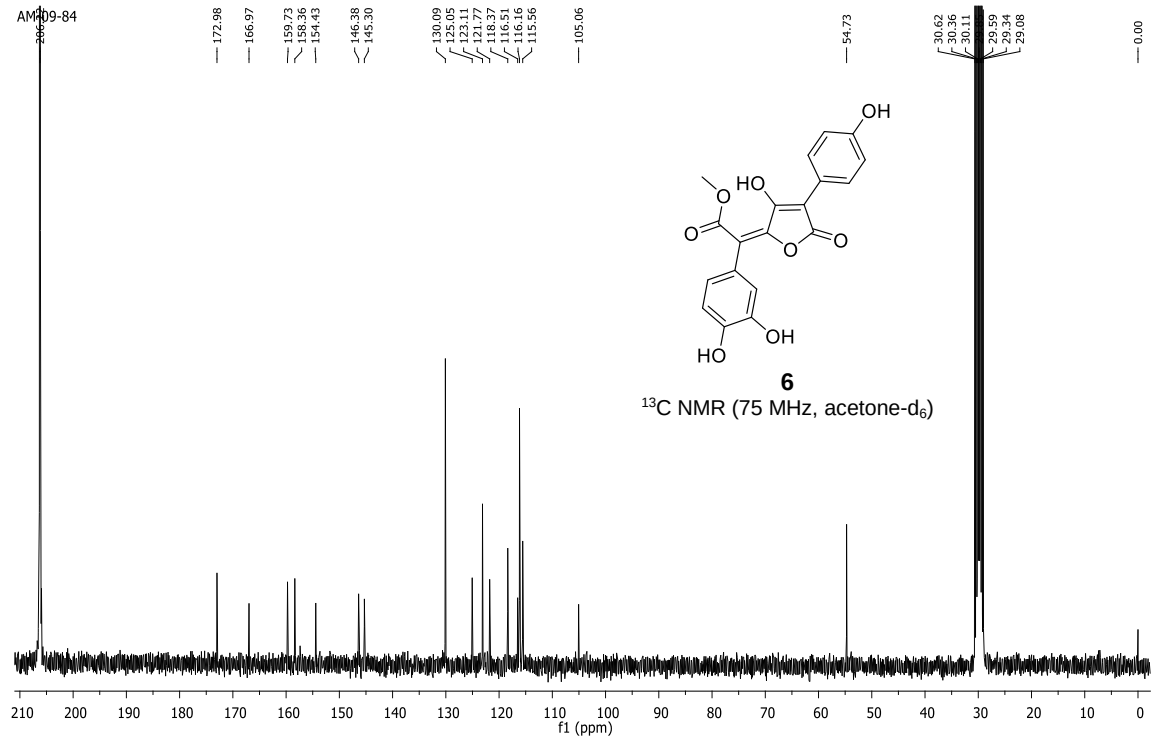
110

^{13}C NMR (75 MHz, $CDCl_3$)



6

^{1}H NMR (500 MHz, acetone-d_6)



6

^{13}C NMR (75 MHz, acetone-d_6)

Chapter 4

Stereoselective Synthesis of Naturally Occurring Pulvinones by Aldol Condensation and Undirected Rh(II)-Catalyzed C-H Insertion Reactions of Diazotetronic Acid

4.1 Introduction

Tetronic acids or 4-hydroxy-5*H*-furan-2-ones are characteristic structural units in many natural products and pharmaceutical compounds.[1] 5-Arylidene-4-hydroxy-3-aryl-5-furan-2(5*H*)-ones constitute a major group of naturally-occurring tetronic acids. Prominent examples of these tetronic acid derviatives[2] are pulvinone (**1**, Figure 4.1), aspulvinone E (**2**), aspulvinone G (**3**), 3',4,4'-trihydroxypulvinone (**4**), aspulvinone A (**5**), aspulvinone C (**6**), aspulvinone B (**7**), aspulvinone D (**8**), aspulvinone H (**9**), aspulvinone F (**10**)[3] and aspulvinone M (**11**).[3] The aspulvinones display a wide range of biological activities[4] which include anticoagulant and anti-inflammatory activities as well as inhibitory activity against *Escherichia coli* and several Gram-negative bacteria. Pulvinones[5] are cellular membrane stabilizers. These compounds prevent complement activation[5] or complement fixation in the immune system by irreversible binding to C1r and C1s, which are proteases in the C1 complex. Pulvinones are yellow pigments, which were first isolated from common larch mushrooms *Suillus grevillei* and the culture filtrate of *Aspergillus terreus*.[5]

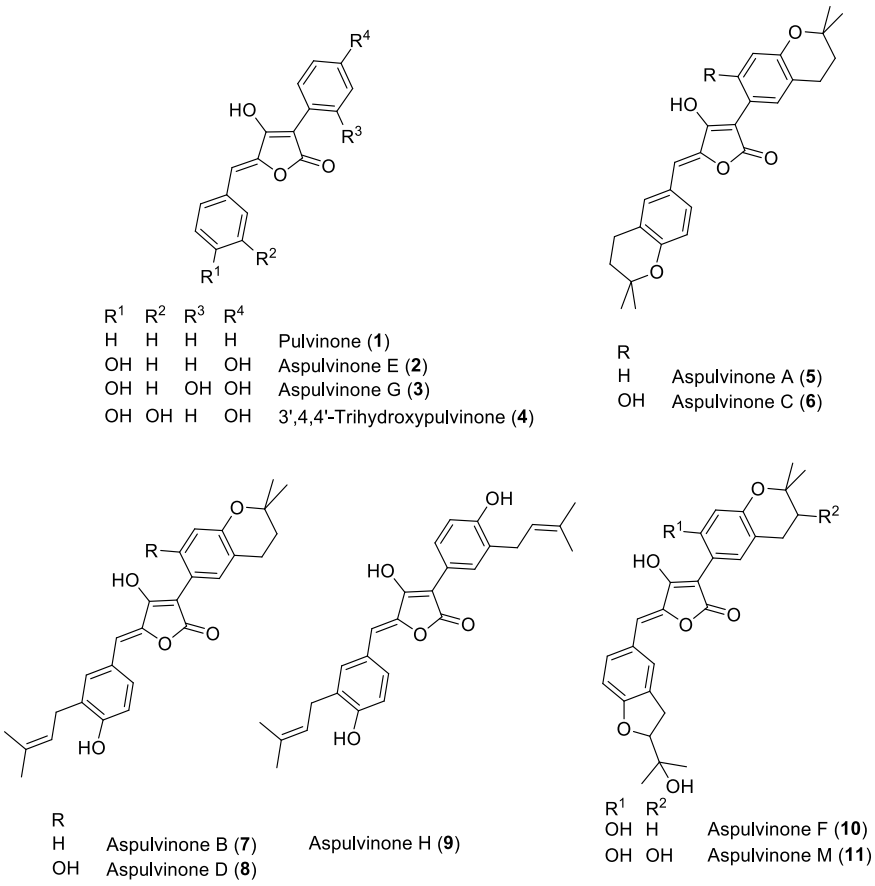


Figure 4.1 Naturally occurring pulvinones

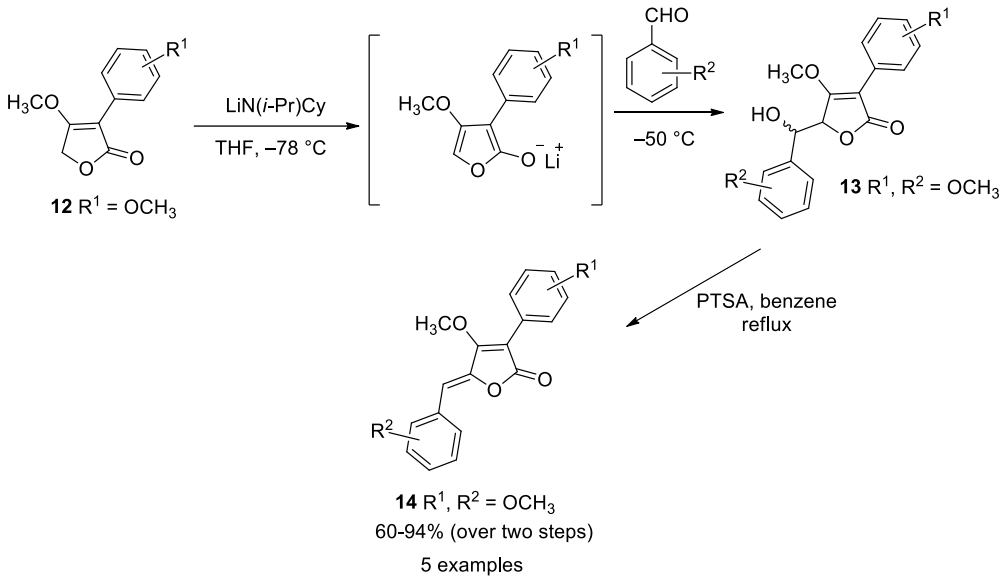
The wide spectrum of biological activities of the pulvinones has led to significant interest in their synthesis and the following section provides a summary of the reported synthesis of natural as well as non-natural pulvinones.

4.2 Known synthetic routes to pulvinones

4.2.1 The Pattenden synthesis of pulvinones

In 1979, Pattenden and coworkers[6] reported the syntheses of pulvinones from *O*-methylated tetronic acids **12** (Scheme 4.01). Metallation of tetronic acids **12** with lithium

N-cyclohexyl-*N*-isopropylamide (LCPA) followed by addition of aryl aldehydes furnished the aldol products (**13**), which were subjected to dehydration in the presence of *p*-toluenesulfonic acid (PTSA) to provide the corresponding pulvinones (**14**) as single diastereomers.

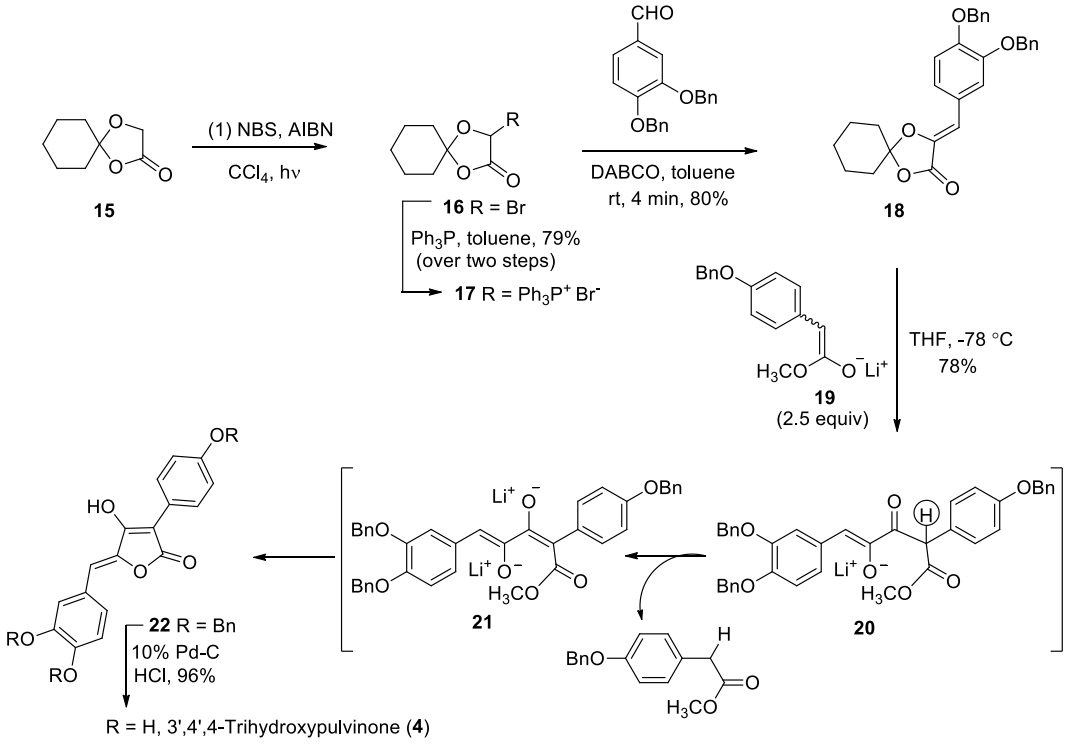


Scheme 4.01

4.2.2 The Ramage synthesis of 3',4',4-trihydroxypulvinone (4)

In 1984, Ramage and coworkers [7] developed a method to synthesize 3',4',4-trihydroxypulvinone (**4**, Scheme 4.02). Bromination of the glycolic acid-derived dioxolanone **15** with *N*-bromosuccinimide (NBS) provided **16**, which was immediately treated with triphenylphosphine in toluene to provide phosphonium salt **17**. Condensation of **17** with 3,4-dibenzyloxybenzaldehyde in the presence of DABCO provided **18**. Claisen condensation of the lithium enolate **19** and alkene **18** provided the tetronic acid derivative **22** as a single diastereomer. **22** was then debenzylated (Pd-C and HCl) to provide 3',4',4-

trihydroxypulvinone (**4**). It is important to mention that 2.5 equivalents of ester enolate **19** were used in the condensation reaction. The first equivalent of **19** opens the dioxolanone ring, resulting in the formation of lithium enolate **20**, and cyclohexanone as the byproduct. The second equivalent forms the lithium bis(enolate) **21** which cyclizes to provide **22**.

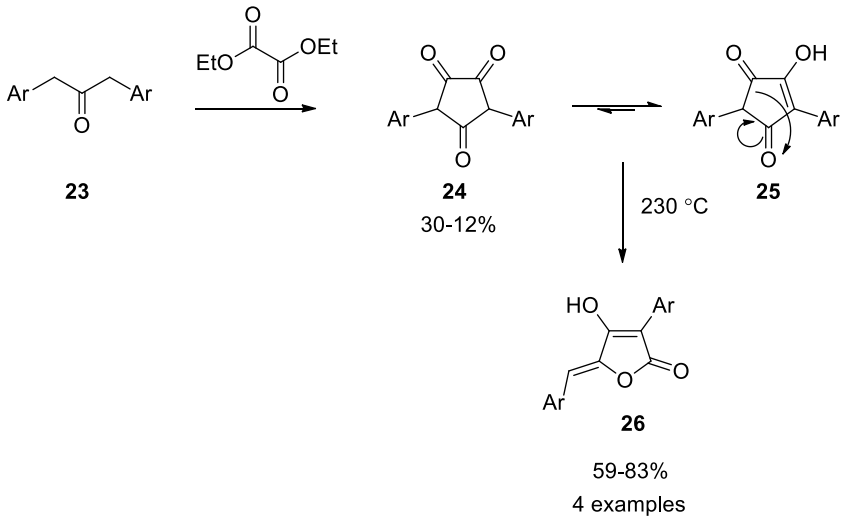


Scheme 4.02

4.2.3 The Campbell syntheses of pulvinones

In 1985, Campbell and coworkers[5] developed two methods for the synthesis of pulvinones. The first approach relies on a thermal [1,3]-sigmatropic rearrangement and the second involves a Wittig reaction as the key transformations.

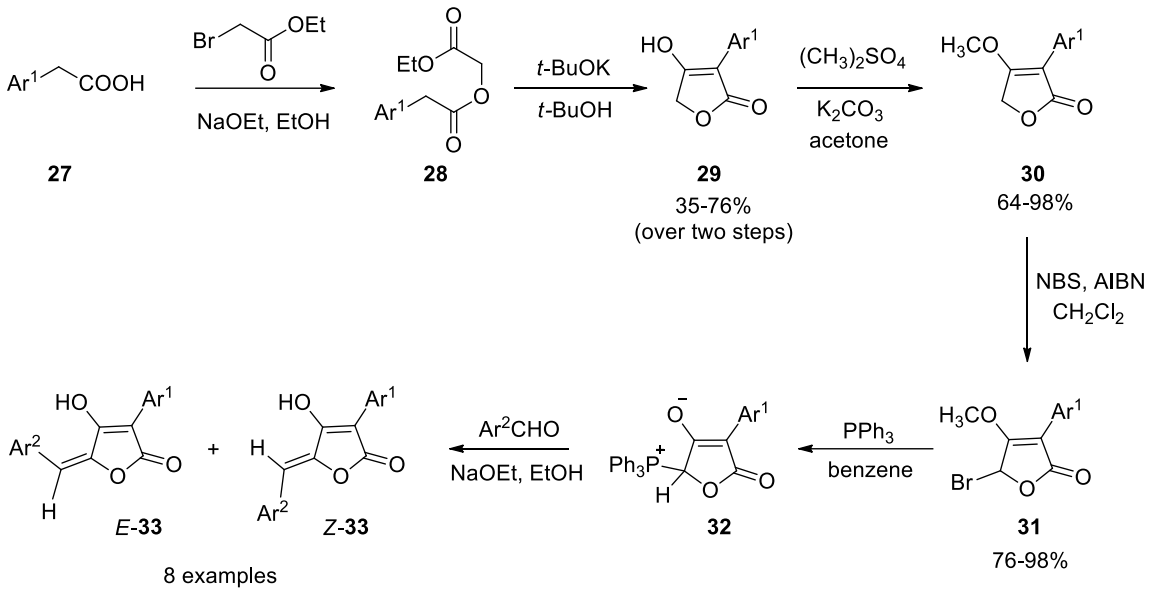
In the first synthesis, 1,3-diarylacetones **23** were condensed with diethyl oxalate to access the symmetrical trione **24** which exists as a tautomeric mixture with the corresponding enol **25**. Heating this mixture at 230 °C provides the pulvinone **26**. Poor yields are obtained when the aryl groups in **23** are *p*, *p*′-disubstituted, and this method is also limited to the syntheses of pulvinones which contain two identical aryl groups (Scheme 4.03).



Scheme 4.03

To overcome these limitations, a procedure that allowed the regiospecific introduction of the two aryl groups was investigated. In this approach, arylacetic acids **27** were treated with ethyl bromoacetate in the presence of sodium ethoxide to give diesters **28** (Scheme 4.04). These diesters were subjected to a Dieckmann-cyclization reaction in the presence of potassium *t*-butoxide to afford 3-aryltetronic acids **29**. Methylation of **29** using dimethyl sulfate followed by bromination with NBS furnished **31** which were then treated with triphenylphosphine to furnish the inner phosphonium salts **32**. Wittig reaction

of **32** with various aryl aldehydes provided a mixture of *E*- **33** and *Z*-**33** pulvinones, with the *Z* isomers as the major products (Scheme 4.04).

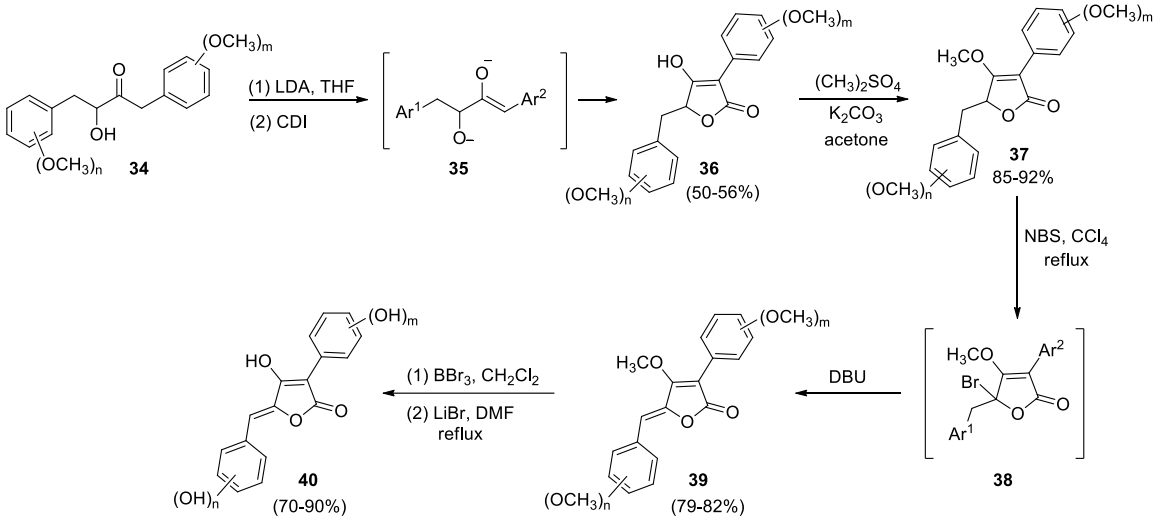


Scheme 4.04

4.2.4 The Gill synthesis of pulvinones

In 1990, Gill and coworkers [8] reported the synthesis of pulvinones from unsymmetrical acyloins (**34**, Scheme 4.05). Alcoholate-enolate dianions **35**, generated *in situ* by deprotonation of the acyloins **34** with lithium diisopropylamide (LDA), were treated with carbonyldiimidazole (CDI) to afford the dihydropulvinones **36**. Methylation of **36** with dimethyl sulfate ($(CH_3)_2SO_4$) provided **37**. The required 5-arylidene functionality was then introduced by bromination of **37** to provide **38**, and subsequent dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the *O*-methyl pulvinones **39** as single diastereomers. Treatment of **39** with BBr_3 cleaved only the phenolic *O*-methyl ethers but not the enolic *O*-methyl ether in **39**. Removal of the enol methyl ether by acid or base

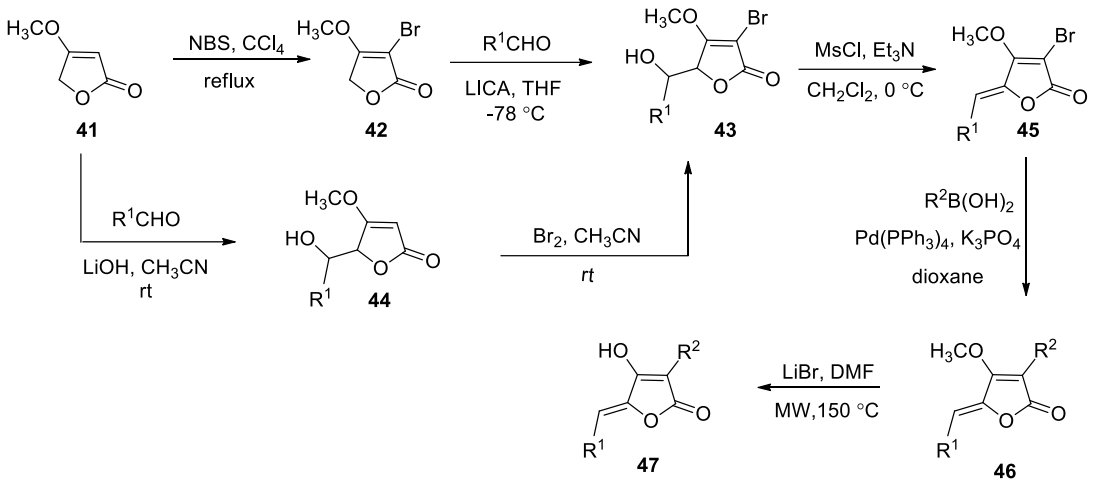
catalyzed hydrolysis was also unsuccessful. However, treatment of **39** with LiBr in DMF under reflux gave the corresponding pulvinones **40**.



Scheme 4.05

4.2.5 The Antane syntheses of pulvinones

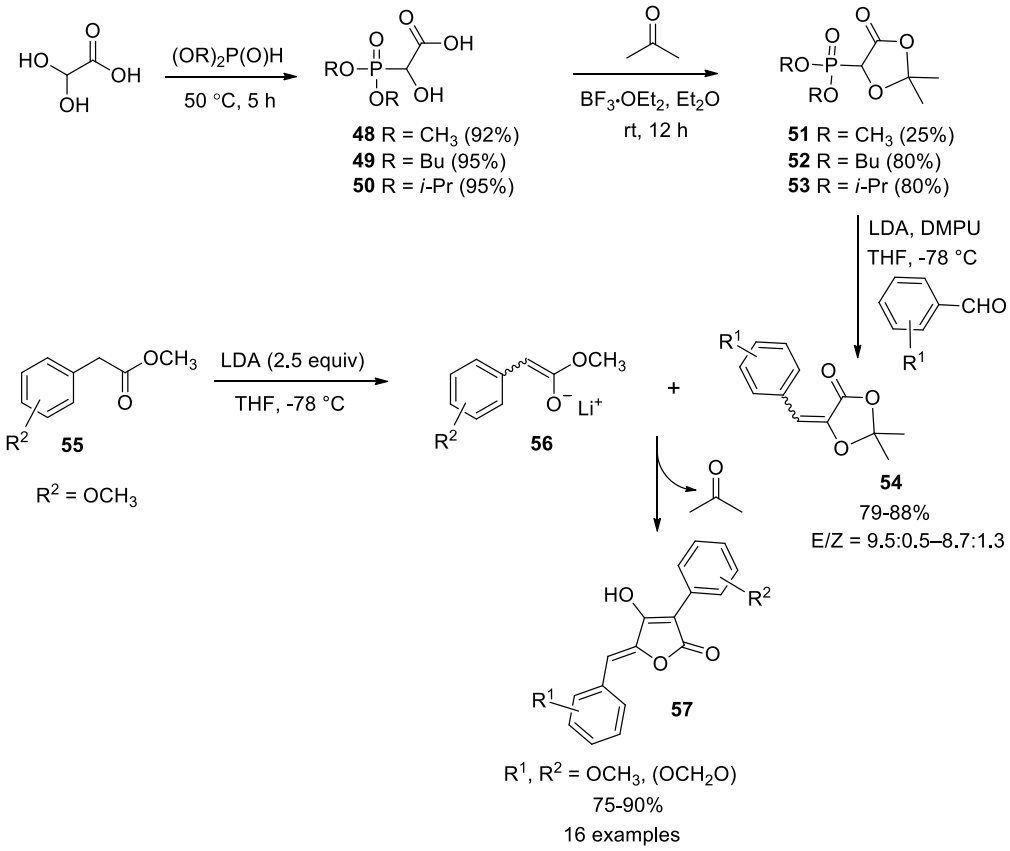
In 2006, Antane and coworkers[9] developed a synthesis of pulvinones by employing a Suzuki-coupling reaction as the key step (Scheme 4.06). Bromination of 4-methoxy-2(5*H*)-furanone (**41**) with NBS gave **42** which was subjected to an aldol reaction with various aldehydes in the presence of lithium isopropyl cyclohexylamide (LICA) to furnish the 5-(hydroxyalkyl) tetronates **43**. Alternatively, tetronates **43** were synthesized from **41** by the aldol reaction followed by bromination. Dehydration of the aldol products **43** by mesylation and elimination provided **45** as the *Z*-isomer. Suzuki-Miyaura cross-coupling of bromoalkenes **45** with various boronic acid derivatives afforded *O*-methyl pulvinones **46** which were demethylated (LiBr, microwave heating at 150 °C) to yield the pulvinones **47**.



Scheme 4.06

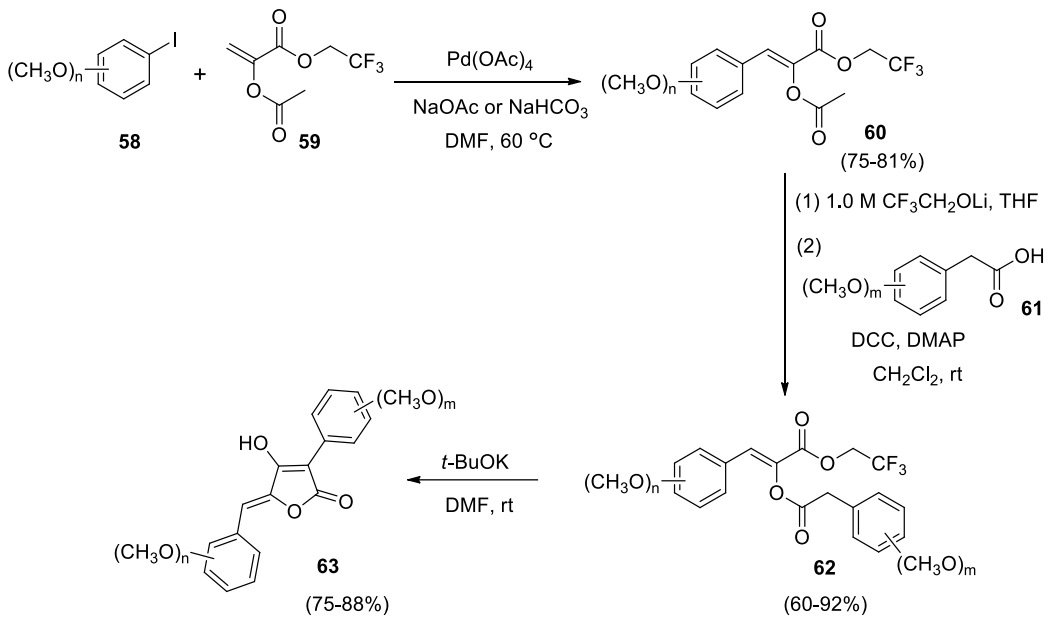
4.2.6 The Brückner syntheses of pulvinones

In 2007, Brückner and coworkers[10] developed a synthesis of pulvinones involving tandem Horner–Wadsworth–Emmons and Claisen condensation reactions as the key transformations (Scheme 4.07). 2,2-Dihydroxyacetic acid (glyoxylic acid hydrate) was treated with dialkyl phosphites to furnish the corresponding dialkyl phosphonates **48**-**50**, which were then reacted with acetone to give dioxolanone-containing dialkyl phosphonates **51-53**. Horner–Wadsworth–Emmons reactions of these phosphonates with a variety of aldehydes in the presence of LDA provided *E*- and *Z*-**54** (*E*-alkene as the major product). In the final step, dioxolanones **54** were subjected to a tandem Claisen condensation with ester enolates **56** (generated *in situ* from alkyl aryl acetates **55** in the presence of LDA) to afford *Z*-pulvinones **57** selectively. The conversion of **51-53** to **57** is according to the Ramage synthesis of pulvinones described in Scheme 4.02.



Scheme 4.07

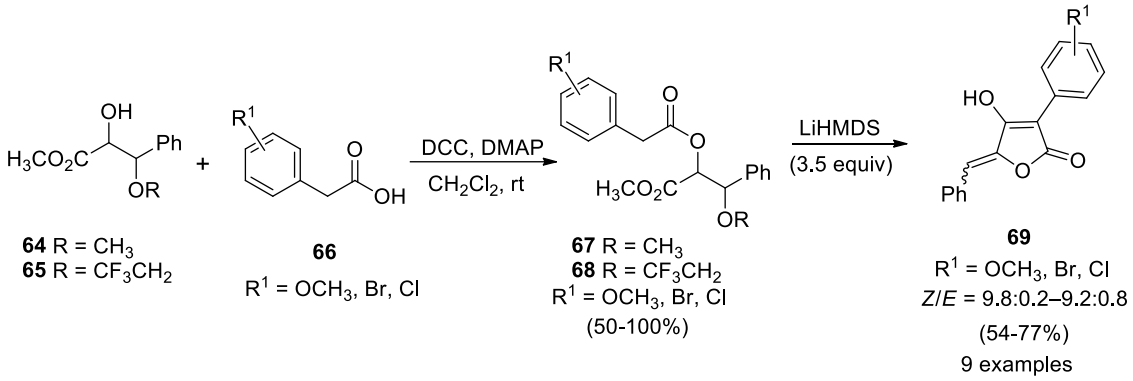
The Brückner group has also reported[2] another approach to the synthesis of pulvinones. This methodology includes Heck alkenylations of iodoarenes, transesterification and Dieckmann cyclization reactions as the key steps (Scheme 4.08). Stereoselective Heck coupling of iodoarenes **58** with trifluoroethyl 2-acetoxyacrylate **59** provided trifluoroethyl (*Z*)-2-acetoxycinnamates **60** which were then subjected to a transesterification reaction with aryl acetic acids **61** to furnish trifluoroethyl (*Z*)-2-(arylacetoxy)cinnamates **62**. Dieckmann cyclization of **62** in the presence potassium *tert*-butoxide (*t*-BuOK) provided the pulvinones **63**.



Scheme 4.08

4.2.7 The Le Gall synthesis of pulvinones

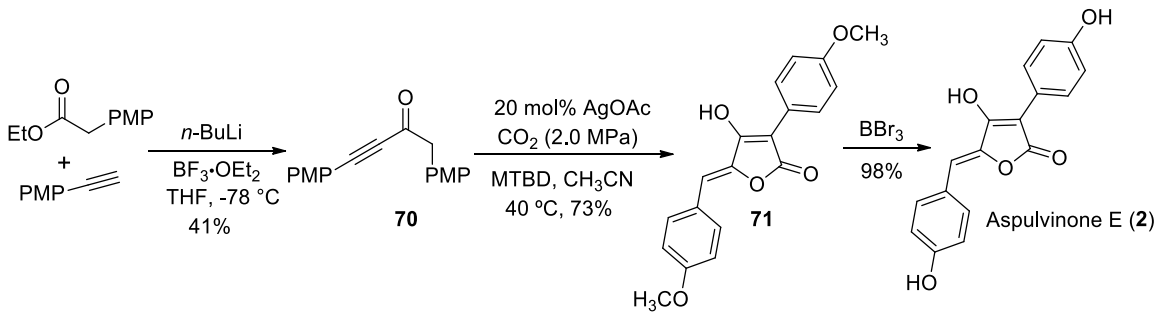
In 2011, Le Gall and coworkers[11] developed a synthetic route to pulvinones *via* a Dieckmann condensation and a *β*-elimination of an alkoxide (Scheme 4.09). Esterification of hydroxy esters **64** and **65** with the arylacetic acid **66** afforded diesters **67** and **68** respectively. These diesters **67-68** were converted to the corresponding pulvinones **69** in the presence of lithium hexamethyldisilazide (LiHMDS) by a Dieckmann condensation and a *β*-elimination of an alkoxide. This procedure generates a mixture of *E*- and *Z*- pulvinones with the *Z*-isomer as the major product.



Scheme 4.09

4.2.8 The Yamada synthesis of aspulvinone E

Yamada and coworkers[12] have recently developed a synthesis of 5-ylidene tetronic acids employing silver-catalyzed reactions of conjugated ynones with CO_2. The procedure was applied in the synthesis of aspulvinone E (**2**, Scheme 4.10). The acylation reaction of (4-methoxyphenyl)acetylene with ethyl (4-methoxyphenyl)acetate in the presence of *n*-BuLi and $BF_3.OEt_2$ provided ynone **70**. The silver-catalyzed reaction of **70** with carbon dioxide (CO_2) provided 5-arylidene tetronic acid **71** which was then demethylated with BBr_3 to give aspulvinone E (**2**).



Scheme 4.10

4.3 Objective

As discussed above, previous reports on the syntheses of 3-aryl-5-arylidene tetronic acid motifs require starting materials that have the specific functionality which required in the target tetronic acids. Most of these methods use aryl acetic acids or alkyl aryl acetates,[2,5,7,10,11, 12] 1,3-diarylacetones,[5] or dibenzyl acyloins[8] as the starting materials. Although the Antane synthesis[9] adds structural diversity by using cross-coupling reactions of bromofuranone (Scheme 4.06), the method requires multiple steps for the synthesis of the key intermediate. Also, although the Yamada synthesis claims to be the shortest route to aspulvinone E, the steps required to synthesize the phenyl acetates and the functionalized acetylene starting materials are ignored in this claim. All of these approaches are therefore limited by the availability of functionalized starting materials and/or advanced synthetic intermediates. In addition, two of the methods described above provide a mixture of *E* and *Z* pulvinones (Scheme 4.04 and 4.09). We therefore decided to develop a synthesis of pulvinones that would overcome these limitations.

As described in Chapter 3 of this thesis, our synthesis[13] of 3-aryl tetronic acids, pulvinic acids and vulpinic acids, employs a highly stereoselective aldol condensation and an undirected intermolecular, rhodium (II) catalyzed, C-H insertion reaction as the pivotal steps. We reasoned that a similar strategy could be applied for the synthesis of natural as well as unnatural pulvinones. Hence, the focus of our strategy for pulvinone synthesis is to introduce the C5 alkylidene/arylidene functionality by a stereoselective aldol condensation of **72** with a series of aldehydes using and installation of the C3 aryl substituent in a single step by a C-H insertion reaction using a diazo functionality (Figure 4.2).

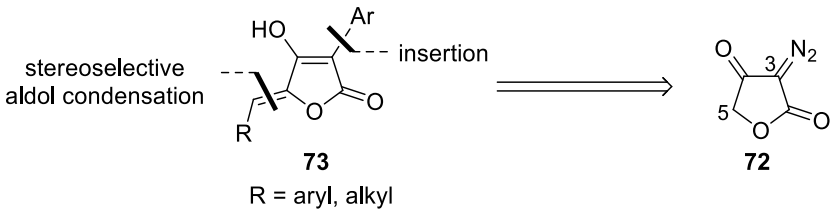


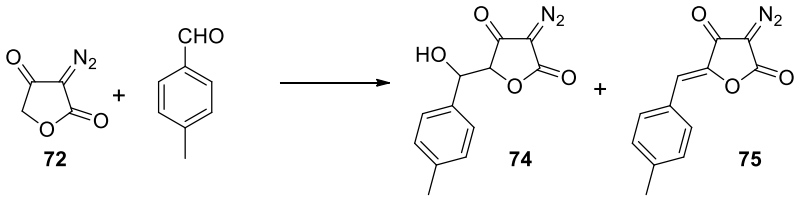
Figure 4.2 Retrosynthetic strategy for synthesis of pulvinones and their derivatives

4.4 Results and Discussion

The initial focus of our synthetic strategy was the stereoselective aldol condensation of **72** to obtain the *Z*-diazo alkenes which are potentially the immediate precursors of the required pulvinones. At the outset, we employed the optimized aldol condensation conditions (Table 4.1, entry 1) that we had developed for the reactions of **72** with benzoylformate esters described in Chapter 3 ($TiCl_4$, Et_3N, Table 3.2, page 246). Somewhat unexpectedly, these conditions provided poor yields of the aldol condensation product of **72** and *p*-tolualdehyde. We therefore conducted an optimization of the aldol condensation reaction of **72** with *p*-tolualdehyde by employing various Lewis acids and bases. Replacing $TiCl_4$ in our previously optimized conditions with $BF_3.OEt_2$ (Table 4.1, entry 2) provided only the aldol product **74** as a mixture of diastereomers (dr = 1:1). Changing the base from triethylamine to heteroaromatic bases such as pyridine, *N*-methylimidazole and 2,4,6-collidine improved the yield of the required product. With pyridine and *N*-methylimidazole (Table 4.1, entries 3 and 4), alkene **75** was obtained in good yields (82% and 77% respectively) but the reaction was slow. However, the reaction with 2,4,6-collidine as the base provided **75** in good yield and also (82%, Table 4.1, entry 5) as a single diastereomer. In addition, this reaction was completed in 80 min. This is the best result from the

optimization studies and the procedure was applied to a variety of aldehydes to provide alkylidene diazotetronates **75-86** (Figure 4.3).

Table 4.1 Optimization of the aldol condensation of **72** with *p*-tolualdehyde.



Entry	Reagents and conditions	74[a]	75[a]
1.	$TiCl_4$, -78 °C, 20 min; Et_3N, -78 °C, 40 min to 0 °C, 1.5 h	–	41
2.	$BF_3.OEt_2$, -78 °C, 20 min; Et_3N, -78 °C, 40 min; 0 °C, 1 h; rt, 1 h	65	–
3.	$TiCl_4$, -78 °C, 20 min; pyridine, -78 °C, 30 min; 0 °C, 2 h; rt, 41 h	–	82
4.	$TiCl_4$, -78 °C, 20 min; *N*-methylimidazole, -78 °C, 30 min; 0 °C, 1 h 20 min; rt, 18 h	–	77
5.	$TiCl_4$, -78 °C, 20 min; 2,4,6-collidine, -78 °C, 30 min; 0 °C, 30 min	–	82

[a]isolated yields

Pleasingly, the aldol condensation reaction of **72** with electron-rich and electron-deficient aromatic aldehydes, as well as aliphatic aldehydes, provided (*Z*)-5-arylidene-3-diazofuran-2,4(3*H*,5*H*)-diones **75-86** as single diastereomers in excellent yields (12 examples, 83% average yield, Figure 4.3). Interestingly, the reaction also worked well with chroman-6-carbaldehyde and 4-((*tert*-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-

yl)benzaldehyde to afford **85** and **86** in 91% and 79% yields, respectively. The only exception was found with **83** which was obtained in relatively low yield (40%). A plausible explanation for the lower yield might be the enolization of cyclopentanecarboxaldehyde under the reaction conditions, and the resulting poor electrophilic reactivity of the enolate with **72**. For reasons that are not known at this time, the reaction of **72** with 4-pyridinecarboxaldehyde was unsuccessful.

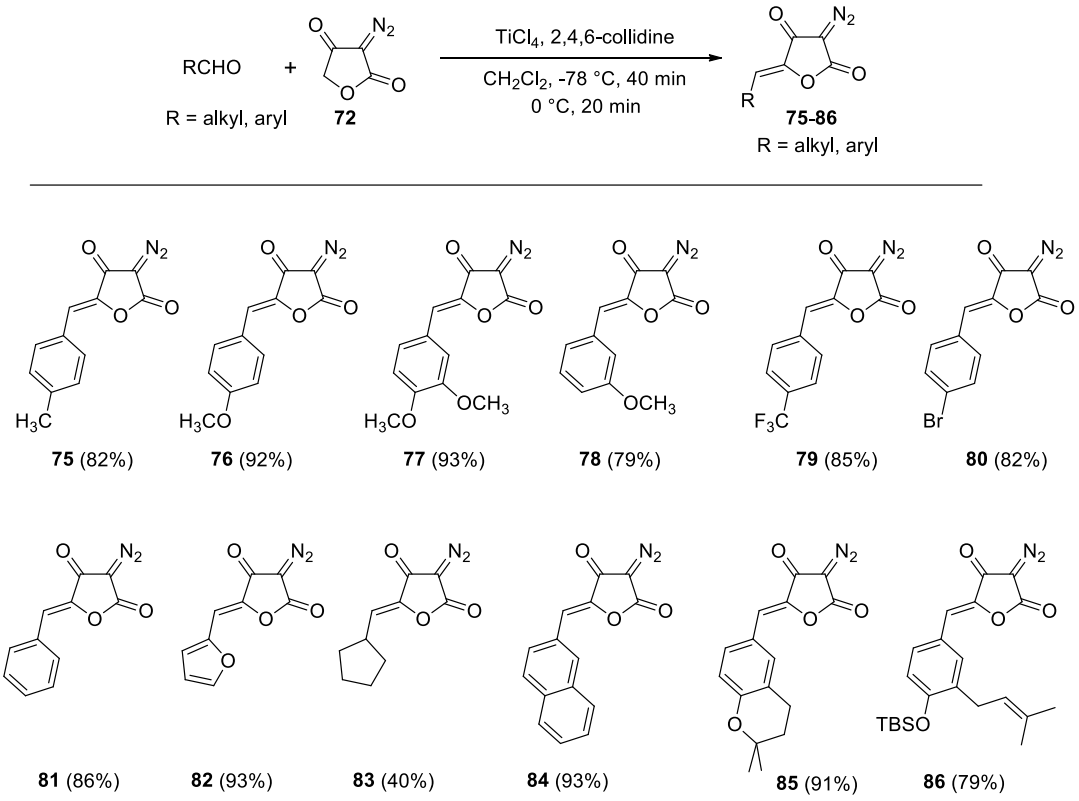


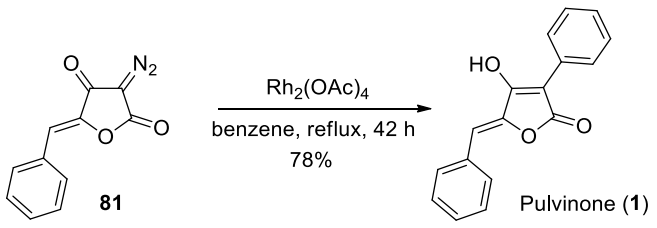
Figure 4.3 Aldol condensation reactions of **72**.

Having established a general method to prepare (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones, the next objective was the introduction of an aryl substituent at C3 to construct the C3-aryl-C5-arylidene/alkylidene tetronic acid (pulvinone)

motif. Accordingly, Rh(II)-catalyzed C-H insertion reactions were examined for selected (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones. In the studies described in Chapter 3 (page 240), two methods were developed for the C-H insertion reactions. In one of the methods, the C-H insertion reactions of diazotetronic acid (**72**) in the presence of $Rh_2(OAc)_4$ in an excess of the arene reacting partner (neat) provided the respective 3-aryl tetronic acids. This procedure (Method A) was used with simple arenes which could be used as a solvent. In the second method, **72** was treated with 4 equivalents of the arene in $PhCF_3$ as a solvent in the presence of catalyst $Rh_2(CF_3CO_2)_4$. This procedure (Method B) was employed for solid arenes. These two methods were employed for the reactions of 5-ylidene diazotetronic acids with a variety of arenes.

4.4.1 Synthesis of naturally occurring pulvinones

With the diazotetronic acid derivative **81** in hand, a C-H insertion reaction was conducted in benzene to afford pulvinone (**1**, 78%, Method A, Scheme 4.11). Spectroscopic data (^{1}H NMR, ^{13}C NMR) of pulvinone (**81**) were identical with those reported in the literature.[5,7,11]



Scheme 4.11 Synthesis of pulvinone (**1**)

4.4.2 Determination of stereochemical configuration of aldol condensation products

Campbell and coworkers[5] studied the geometry of the pulvinones and confirmed the stereochemistry of the exocyclic alkene. The *Z*-**1** and *E*-**1** geometrical isomers were synthesized from the corresponding inner phosphonium salts (**32**) by the Wittig reaction (Scheme 4.04). The stereochemical configurations of the olefins obtained were deduced by a comparison of the chemical shifts of characteristic protons and carbons in stereochemically pure *Z*-**1** and *E*-**1** products and in the *O*-acetylpulvinones *Z*-**87** and *E*-**87** using ^{1}H NMR and ^{13}C NMR spectroscopy.

For the pulvinones *Z*-**1** and *E*-**1**, ^{1}H NMR signals for the alkene protons at C6 in *Z*-**1** appeared at δ 6.75, whereas in the case of *E*-**1** this proton appears at δ 6.80 (Figure 4.3). Similarly, in the ^{13}C NMR, the signals for C3 and C6 in *Z*-**1** are at δ 100.2 and δ 107.5 respectively, whereas for *E*-**1** these signals appeared at δ 104.9 and δ 114.5 respectively. This study concluded that the significant difference in chemical shifts for the *E*-**1** and Z-**1** pulvinones can be used for assigning stereochemistry. The pulvinone (**1**) obtained in our study (Scheme 4.11) exhibited ^{1}H and ^{13}C chemical shifts that are identical (^{1}H NMR proton at C6 δ 6.75 and ^{13}C NMR C3, C6 at δ 100.1, 107.6 respectively) to those reported by Campbell for *Z*-**1** (Figure 4.4). Hence, **1** obtained by our procedure was assigned the *Z* stereochemistry.

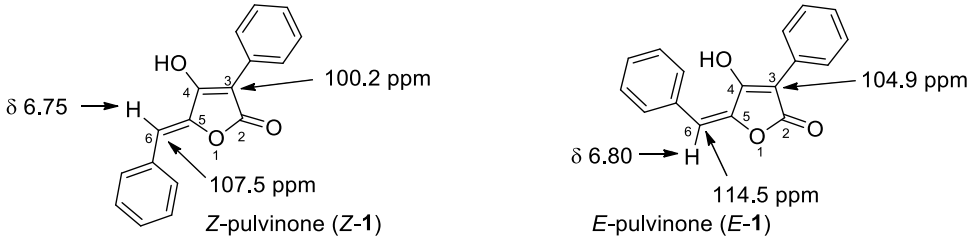


Figure 4.4 ^{1}H and ^{13}C chemical shifts of *Z*- and *E*- pulvinones

Additional evidence for the stereochemical assignment was obtained by conversion of *Z*-**1** to *Z*-**87** by acetylation. Campbell has also reported[5] that in *Z*-**87** the alkene proton at C6 and acetyl group appeared at δ 6.04 and δ 2.35 respectively, whereas in *E*-**87**, the alkene proton at C6 and the acetyl group appeared at δ 6.88 and δ 1.67 respectively (Figure 4.5). Notably, the acetyl group in *E*-**87** (δ 1.67) experiences an upfield shift due to anisotropic shielding by the phenyl group, as compared to the acetyl group in *Z*-**87** (δ 2.35). The *Z*-**87** which was prepared by the acetylation of **1** obtained by our aldol condensation procedure had key spectroscopic data (C6-*H* δ 6.08 and C(O)CH_3 δ 2.42) which matched the data reported for *Z*-**87** (Figure 4.5). Based on these observations, the geometry of the aldol condensation products (alkenes) in our studies, which are the immediate precursors of pulvinones, was assigned as *Z*.

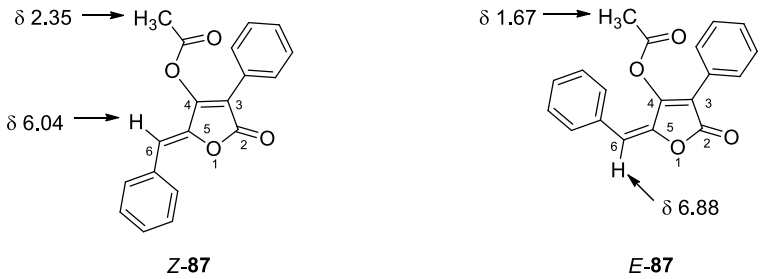
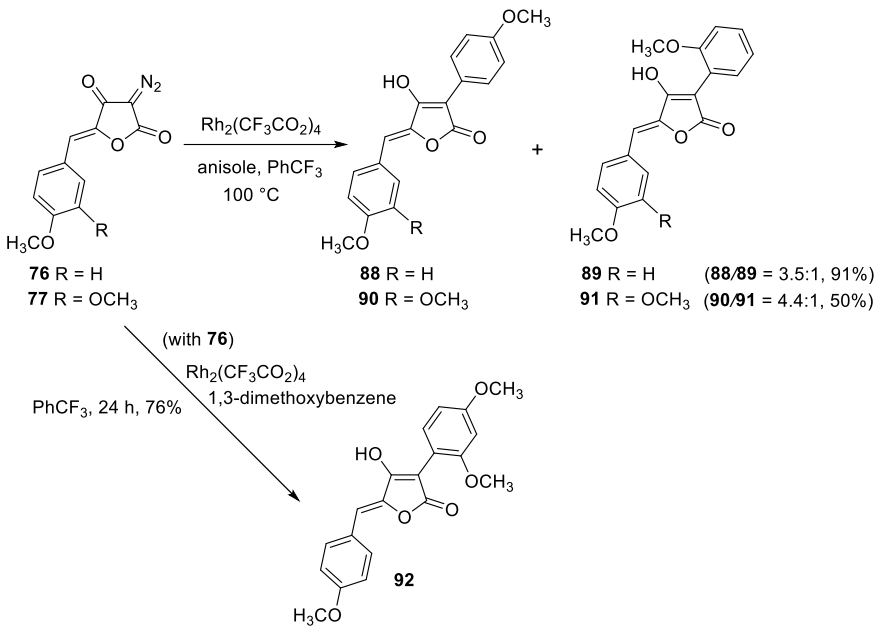


Figure 4.5 ^{1}H chemical shifts of *Z*-**87** and *E*-**87**

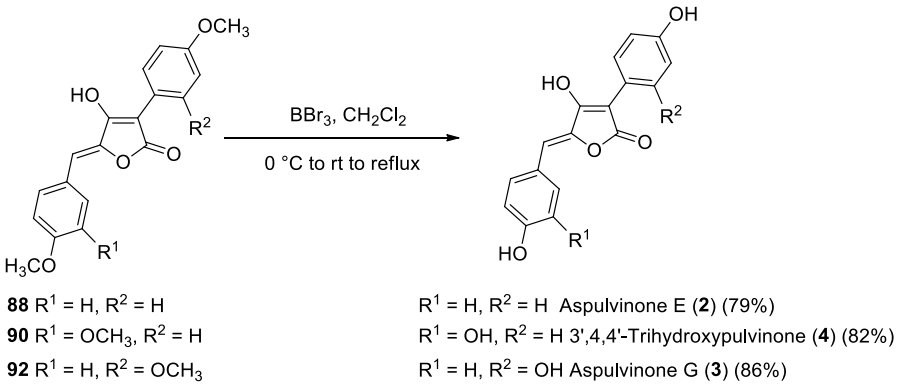
Next, the synthesis of aspulvinone E (**2**), aspulvinone G (**3**), and 3',4,4'-trihydroxypulvinone (**4**) was investigated. The Rh(II)-catalyzed C-H insertion reaction of **76** with anisole (Method B) provided the regioisomeric insertion products **88** and **89** (**88**/**89** = 3.5:1, 91%). A similar reaction of **77** provided **90** and **91** (**90**/**91** = 4.4:1, 50%, Scheme 4.12). The regioisomeric products (**88** and **89**, **90** and **91**) were easily separated by flash

column chromatography. A similar C-H insertion reaction of **76** with 1,3-dimethoxybenzene (Method B) provided **92** (76%, Scheme 4.12).



Scheme 4.12

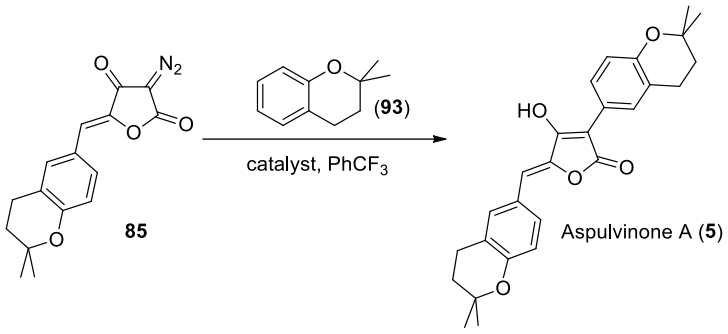
Following the literature procedure,[2] the pulvinones **88**, **90** and **92** were demethylated with BBr_3 to furnish aspulvinone E (**2**), 3',4,4'-trihydroxypulvinone (**4**) and aspulvinone G (**3**) in 79%, 82% and 86% yields respectively (Scheme 4.13).



Scheme 4.13 Synthesis pulvinones **2**, **4** and **3**

Having achieved the synthesis of the naturally ocuring pulvinones **1**, **2**, **3** and **4**, we next targeted the naturally occurring aspulvinone A (**5**), aspulvinone B (**7**), aspulvinone C (**6**) and aspulvinone D (**8**). In initial studies, $Rh_2(CF_3COO)_4$ (Table 4.2, entry 1) and $Rh_2(OAc)_4$ (Table 4.2, entry 2) were screened as catalysts in the C-H insertion reactions of **85** with chroman **93**. However, in both cases, poor yields (29%, 38% respectively) of **5** were observed. Changing the catalyst to $Rh_2(esp)_2$ (Du Bois's catalyst, 1 mol%) improved the yield of aspulvinone A (**5**) to 60% (Table 4.2, entry 4). These conditions (4 equivalents of **93**, $Rh_2(esp)_2$ in $PhCF_3$ at 50 ºC, Method C) were also used for other insertion reactions of arylidene tetronates and chromans.

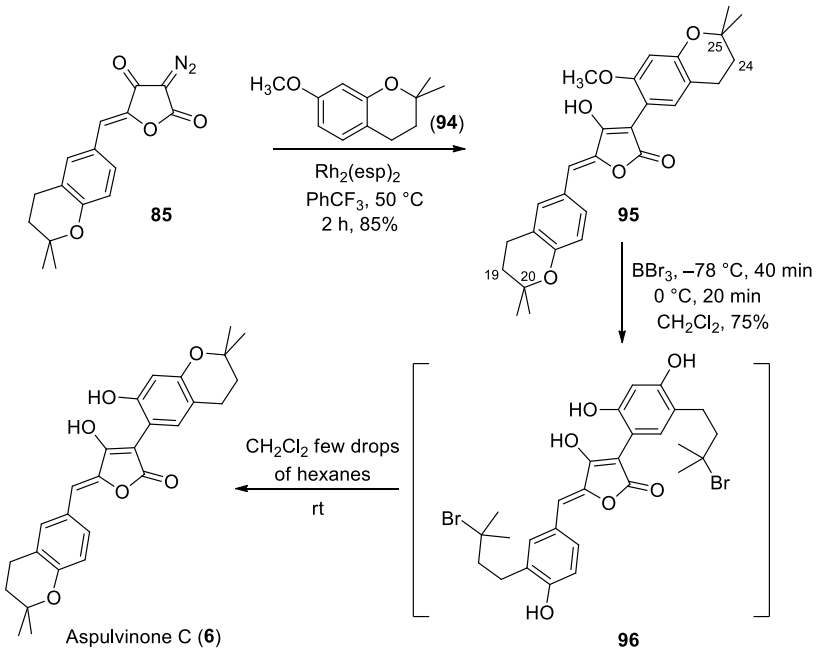
Table 4.2 Optimization of C-H insertion reaction of chroman **93**



Entry	Catalyst	Temp (ºC)	Time (h)	5 (%)[a]
1	$Rh_2(CF_3CO_2)_4$	100	7.5	29
2	$Rh_2(AcO)_4$	100	25	38
3	$Rh_2(esp)_2$	100	1.5	58
4	$Rh_2(esp)_2$	50	6	60

[a]isolated yields

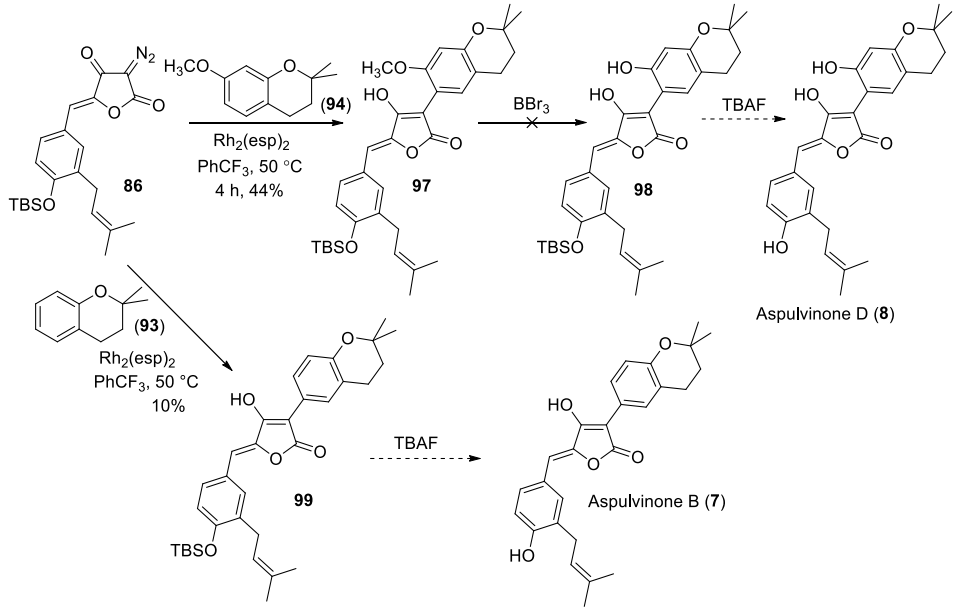
Thus, using the optimized conditions for the chroman insertion, diazotetronate **85** was treated with 7-methoxy-2,2-dimethylchromane (**94**) using catalyst $Rh_2(esp)_2$ (Method C) to give **95** in 85% yield. Demethylation of **95** with BBr_3 provided aspulvinone C (**6**, 75%, Scheme 4.14). Notably, during this reaction BBr_3 demethylated the O-CH_3 on chroman and simultaneously cleaved the O─C25 and O─C20 bonds to provide the dibromo trihydroxy compound **96** as an intermediate (confirmed by ^1H NMR and HRMS). Surprisingly, the intermediate **96** formed aspulvinone C (**6**) in 75% yield by leaving the crude demethylation product at room temperature. This unusually facile substitution reaction involves a tertiary alkyl bromide as the electrophile and a phenolic OH group as the nucleophile. A similar reaction of a 1,3-dimethoxy-2-prenyl aryl motif has been reported by Eicher[14] (demethylation with BBr_3 and subsequent cyclization with a prenyl group to provide a chroman skeleton at -78 ºC).



Scheme 4.14 Synthesis of aspulvinone C (**6**)

Next, the syntheses of aspulvinone B (**7**) and D (**8**) were explored using the same strategy. $Rh_2(esp)_2$-catalyzed (Method C) C-H insertion of **86** with chroman **94** provided **97** in 44% (Scheme 4.15). Unfortunately, the attempted demethylation of **97** with BBr_3 was unsuccessful. Notably, examination of the ^1H NMR of the crude reaction product indicated that the double bond of the prenyl group in **97** had reacted but the methoxy and silyl ether functional groups remained intact during the reaction. Investigations of this reaction employing other demethylating reagents and conditions are ongoing.

In related studies, the insertion reaction of **86** and chroman **93** provided the required product **99** in very low yield (~10%). Notably, desilylation (TBS removal) of **99** would provide aspulvinone B (**7**), and the demethylation and desilylation of **97** will provide aspulvinone D (**8**). Although we are tantalizingly close to these targets, these synthetic efforts were discontinued due to the problems encountered with the deceptively simple deprotection chemistry of **97** and **99** (Scheme 4.15).



Scheme 4.15 Attempted synthesis of aspulvinones B (**7**) and D (**8**)

4.4.3 Other synthetic approaches aspulvinones B (7) and D (8)

Simultaneously with the studies described above, an alternative approach to aspulvinones B (**7**) and D (**8**) was also examined. We reasoned that these natural products could be accessed from tetronic acids **102** and **103** by aldol condensation with aldehydes **100** and **101** respectively. In addition to changing the sequence of events in the pulvinone synthesis (insertion before aldol condensation) this study was planned to also avoid the problematic protecting groups (methyl ether and TBS ether) encountered in the previous studies (Figure 4.6). Thus, an acetate was used instead of the methyl ether and a benzyl ether replaced the TBS ether.

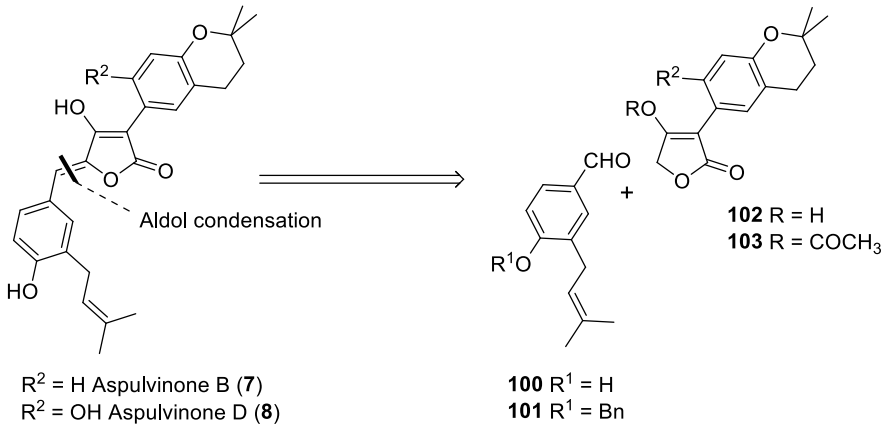
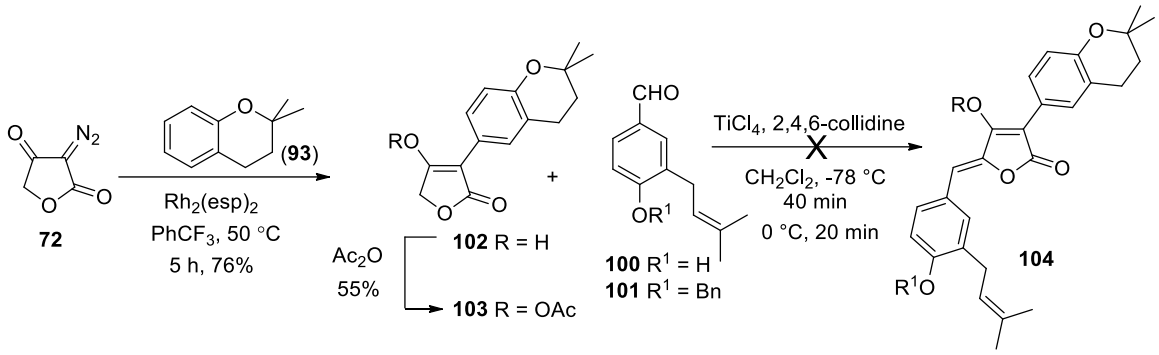


Figure 4.6 Retrosynthetic route for synthesis of aspulvinones B (**7**) and D (**8**)

Accordingly, the C-H insertion reaction was performed between diazotetronate **72** and chroman **93** to afford **102** in 76% which was then protected to provide the acetate **103** in 55% yield (Scheme 4.16). Aldol condensation reactions of **102** and **103** with unprotected aldehyde **100** (free phenolic OH group) under our optimized conditions (Table 4.1, entry 5) did not provide the expected product **104** (R^1 = H). Similarly, the reaction of **103** with

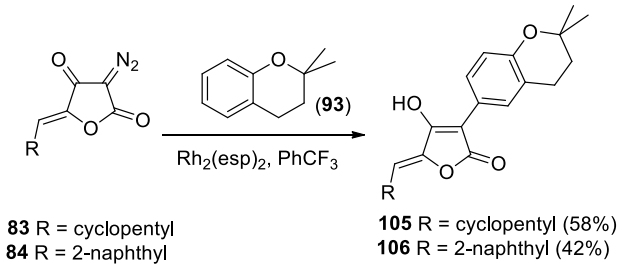
101 (*O*-benzyl **100**) also failed. Unfortunately, these reactions generated complex mixtures which did not contain any of the required products. Investigations on these aldol reactions under various other conditions are ongoing.



Scheme 4.16 Synthesis of aspulvinone B (**7**)

4.4.4 Synthesis of unnatural pulvinones

In related studies, the synthesis of unnatural pulvinones (pulvinone analogues) was also investigated. The C-H insertions of **83** and **84** with chroman **93** provided the corresponding pulvinone derivatives **105** and **106** in 58% and 42% yields respectively (Scheme 4.17).



Scheme 4.17 Synthesis of pulvinone analogues

In addition to the stereochemical observations described in Section 4.4.2 (page 327), the ^{1}H and ^{13}C NMR spectroscopic data of compounds **2**, **3**, **4**, **5**, **6**, **88**, **90** and **92** are

in complete agreement with that reported for the *Z*-isomers in the literature. These observations also confirm the geometry of the aldol condensation products as *Z*. A detailed comparison of the spectroscopic data is provided in the experimental section.

4.5 Conclusion

In conclusion, a facile and versatile methodology has been developed to synthesize naturally occurring pulvinones and their derivatives. The syntheses of pulvinone (**1**), aspluvinone A (**5**) and pulvinone derivatives **105**, **106** were achieved in two steps from diazo tetronic acid (**72**). Similarly, syntheses of aspulvinone E (**2**), aspulvinone G (**3**), 3',4,4'-trihydroxypulvinone (**4**), aspulvinone C (**6**) were accomplished in three steps from **72**. This methodology provides direct access to a wide range of stereoisomerically pure (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones and 5-arylidene-4-hydroxy-3-aryl-5-furan-2(5*H*)-ones. We anticipate that our modular strategy will be useful for preparing natural product-like libraries of pulvinones by systematic variation of the C3 aryl group and the aryl/alkyl group at C5. Investigations on the synthesis of aspulvinone B (**7**) and D (**8**) are ongoing.

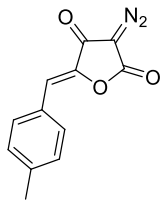
4.6 Experimental Section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 was distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 6200 LC/MSD (TOF) chromatographic system.

General procedure for the aldol condensation of diazotetronate 72 and aldehydes:

To a solution of **72** (1 equiv) and aldehyde (1 equiv) in CH_2Cl_2 was added $TiCl_4$ (3 equiv) at -78 °C. The solution was stirred for 20 min, 2,4,6-collidine (3 equiv) was added and the mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. Saturated aqueous NH_4Cl (~3 mL) was added followed by cold water (~2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide the alkylidene diazotetronates **75-86**.

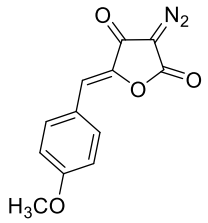
(*Z*)-3-Diazo-5-(4-methylbenzylidene)furan-2,4(3*H*,5*H*)-dione (75):



The reaction of **72** (126 mg, 1.00 mmol), 4-methylbenzaldehyde (118 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2, 4, 6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 188 mg (82%) of **75** as a white solid.

R_f = 0.32 (hexanes/EtOAc, 8.5:1.5); mp: 147-150 °C; IR (neat): 2157, 1758, 1689, 1634, 1602, 1362, 1339, 1313, 1251, 1078, 1048, 962, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.23 (d, 2H, *J* = 8.1 Hz, Ar*H*), 6.68 (s, 1H, ArC*H*=C), 2.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (*C*=O), 160.5 (O*C*=O), 141.6 (O-*C*=CHAr or ArC_{ipso}), 141.3 (O-*C*=CHAr or ArC_{ipso}), 131.6 (2 × Ar*C*), 129.9 (2 × Ar*C*), 128.3 (ArC_{ipso}), 112.2 (Ar*C*H=C), 21.8 (*C*H_3); HRMS (APPI, pos.): *m/z* 228.0537 (228.0535 calc. for $C_{12}H_8N_2O_3$, $(M)^+$).

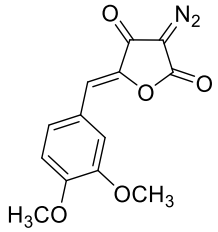
(*Z*)-3-Diazo-5-(4-methoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (76):



The reaction of **72** (126 mg, 1.00 mmol), 4-methoxybenzaldehyde (121 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2,4,6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (6 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 4:1), 224 mg (92%) of **76** as a yellow solid.

R_f = 0.33 (hexanes/EtOAc, 7:3); mp: 141-145 °C; IR (neat): 2970, 2917, 2845, 2158, 1774, 1690, 1646, 1598, 1565, 1508, 1366, 1341, 1305, 1250, 1174, 1134, 1070, 1021, 957 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.94 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 3.86 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 161.4 (O*C*=O or ArC_{ipso}), 160.4 (O*C*=O or ArC_{ipso}), 140.5 (O-*C*=CHAr), 133.4 (2 × Ar*C*), 123.7 (ArC_{ipso}), 114.5 (2 × Ar*C*), 112.0 (Ar*C*H=C), 55.4 (O*C*H_3); HRMS (APPI, pos.): *m/z* 244.0484 (244.0484 calc. for $C_{12}H_8N_2O_4$, $(M)^+$).

(*Z*)-3-Diazo-5-(3,4-dimethoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (77):

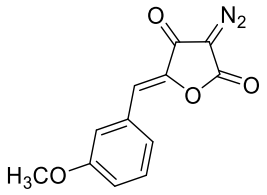


The reaction of **72** (80 mg, 0.64 mmol), 3,4-dimethoxybenzaldehyde (106 mg, 0.640 mmol), $TiCl_4$ (0.21 mL, 1.9 mmol) and 2,4,6-collidine (0.25 mL, 1.9 mmol) in CH_2Cl_2 (4 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3 to 1:1), 161 mg (92%) of **77** as a yellow solid.

R_f = 0.19 (hexanes/EtOAc, 7:3); mp: 177-183 °C; IR (neat): 2961, 2936, 2913, 2836, 2143, 1779, 1693, 1643, 1594, 1513, 1360, 1321, 1266, 1219, 1145, 1129, 1081, 1063, 1018, 979, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1H, Ar*H*), 7.35 (dd, 1H, *J* = 8.6, 2.0 Hz, Ar*H*), 6.91 (d, 1H, *J* = 8.6 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 3.94 (s, 6H, 2 × OCH_3); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.5 (O*C*=O), 151.4 (ArC_{ipso}), 149.3 (ArC_{ipso}), 140.7 (O-*C*=CHAr), 126.2 (Ar*C*), 124.1 (ArC_{ipso}), 113.5 (Ar*C* or Ar*C*H=C), 112.4 (Ar*C* or Ar*C*H=C), 111.3 (Ar*C* or Ar*C*H=C), 56.1 (2 × O*C*H_3); HRMS (APPI, pos.): *m*/*z* 274.0597 (274.0590 calc for $C_{13}H_{10}N_2O_5$ $(M)^+$).

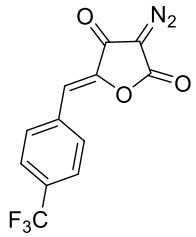
(*Z*)-3-Diazo-5-(3-methoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (78):



The reaction of **72** (150 mg, 1.19 mmol), 3-methoxybenzaldehyde (145 µL, 1.19 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 7:3), 231 mg (79%) of **78** as a yellow solid.

R_f = 0.46 (hexanes/EtOAc, 7:3); mp: 159-161°C; IR (neat): 2923, 2844, 2132, 1764, 1705, 1647, 1582, 1357, 1302, 1215, 1176, 1092, 1074, 1036, 981, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H, Ar*H*), 7.31-7.28 (m, 1H, Ar*H*), 7.00-6.92 (m, 1H, Ar*H*), 6.65 (s, 1H, ArC*H*=C), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 160.1 (O*C*=O or ArC_{ipso}), 159.8 (O*C*=O or ArC_{ipso}), 142.1 (O-*C*=CHAr), 132.1 (ArC_{ipso}), 129.9 (Ar*C*), 124.1 (Ar*C*), 116.6 (Ar*C*), 116.0 (Ar*C*), 111.7 (Ar*C*H=C), 55.4 (O*C*H_3); HRMS (APPI, pos.): *m/z* 244.0480 (244.0484 calc. for $C_{12}H_8N_2O_4$, $(M)^+$).

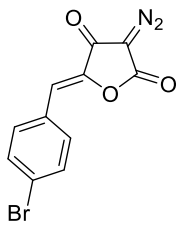
(*Z*)-3-Diazo-5-(4-(trifluoromethyl)benzylidene)furan-2,4(3*H*,5*H*)-dione (79):



The reaction of **72** (126 mg, 1.00 mmol), 4-(trifluoromethyl)benzaldehyde (134 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2,4,6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5 to 4:1), 239 mg (85%) of **79** as a yellow solid.

R_f = 0.56 (hexanes/EtOAc, 7:3); mp: 158-162 °C; IR (neat): 3072, 2924, 2168, 1783, 1710, 1653, 1355, 1317, 1170, 1120, 1045, 1013, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.65 (d, 2H, *J* = 8.3 Hz, Ar*H*), 6.67 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (*C*=O), 159.8 (O*C*=O), 143.4 (O-*C*=CHAr), 134.3 (q, $^5J_{C\text{-}F}$ = 1.4 Hz, ArC_{ipso}), 131.6 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, ArC_{ipso}), 131.3 (2 × Ar*C*), 125.85 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar*C*), 123.7 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, *C*F_3), 109.5 (Ar*C*H=C); HRMS (APPI, neg.): *m/z* 282.0254 (282.0252 calc. for $C_{12}H_5F_3N_2O_3$, $(M)^-$) and 341.0415 (341.0385 calc. for $C_{14}H_8F_3N_2O_5$, $(M+CH_3COO)^-$).

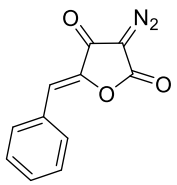
(*Z*)-5-(4-Bromobenzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (80):



The reaction of **72** (150 mg, 1.19 mmol), 4-bromobenzaldehyde (220 mg, 1.19 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5 to 4:1), 287 mg (82%) of **80** as a yellow solid.

R_f = 0.36 (hexanes/EtOAc, 7:3); mp: 214-218 °C; IR (neat): 2163, 1780, 1702, 1638, 1579, 1484, 1354, 1306, 1244, 1131, 1064, 1045, 1003, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.55 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.62 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (*C*=O), 159.9 (O*C*=O), 142.3 (O-*C*=CHAr), 132.7 (2 × Ar*C*), 132.3 (2 × Ar*C*), 129.8 (ArC_{ipso}), 125.0 (ArC_{ipso}), 110.4 (Ar*C*H=C); HRMS (APPI, pos.): *m*/*z* 291.9481 (291.9484 calc. for $C_{11}H_5{}^{79}BrN_2O_3$, $(M)^+$) and 293.9455 (293.9463 calc. for $C_{11}H_5{}^{81}BrN_2O_3$, $(M)^+$).

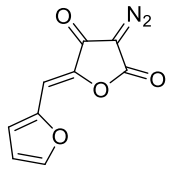
(*Z*)-5-Benzylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (81):



The reaction of **72** (70 mg, 0.56 mmol), benzaldehyde (57 μL, 0.56 mmol), $TiCl_4$ (0.18 mL, 1.7 mmol) and 2,4,6-collidine (0.22 mL, 1.7 mmol) in CH_2Cl_2 (3 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5), 104 mg (87%) of **81** as a white solid.

R_f = 0.51 (hexanes/EtOAc, 7:3); mp: 147-154 °C; IR (neat): 2921, 2852, 2151, 1763, 1699, 1639, 1358, 1337, 1244, 1082, 1051, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.81-7.72 (m, 2H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 6.69 (s, 1H, PhC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (*C*=O), 160.3 (O*C*=O), 142.1 (PhHC=*C*-O), 131.5 (2 × Ar*C*), 131.0 (ArC_{ipso}), 130.5 (Ar*C*), 129.1 (2 × Ar*C*), 111.9 (Ph*C*H=C); HRMS (APPI, pos.): *m/z* 214.0378 (214.0378 calc. for $C_{11}H_6N_2O_3$, $(M)^+$).

(*Z*)-3-Diazo-5-(furan-2-ylmethylene)furan-2,4(3*H*,5*H*)-dione (82):

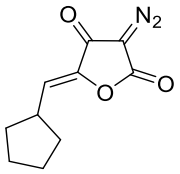


The reaction of **72** (150 mg, 1.19 mmol), 2-furaldehyde (99 μL, 1.2 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 8.5:1.5), 227 mg (93%) of **82** as an orange-yellow solid.

R_f = 0.29 (hexanes/EtOAc, 9:1); mp: 163-167 °C; IR (neat): 2923, 2853, 2166, 1761, 1698, 1641, 1353, 1315, 1242, 1070, 1014, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, 1H, *J* = 1.7, 0.5 Hz, Ar*H*), 7.03 (br dt, 1H, *J* = 3.5, 0.5 Hz, Ar*H*), 6.70 (br s, 1H, ArC*H*=C),

6.57 (ddd, 1H, J = 3.5, 1.7, 0.5 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8 (*C*=O), 160.0 (O*C*=O), 147.5 (O-*C*=CHAr or ArC_{ipso}), 145.6 (Ar*C*), 139.8 (O-*C*=CHAr or ArC_{ipso}), 117.6 (Ar*C*), 113.2 (Ar*C*), 100.5 (Ar*C*H=C); HRMS (APPI, pos.): *m/z* 204.0168 (204.0171 calc. for $C_9H_4N_2O_4$, $(M)^+$)

(*Z*)-5-(Cyclopentylmethylene)-3-diazofuran-2,4(3*H*,5*H*)-dione (83):

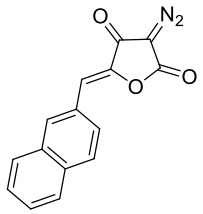


To a solution of **72** (150 mg, 1.19 mmol) in CH_2Cl_2 (4 mL) was added $TiCl_4$ (0.39 mL, 3.57 mmol) at -78 °C and the solution was stirred for 20 min. To the mixture was added 2,4,6-collidine (0.47 mL, 3.6 mmol) followed by dropwise addition of cyclopentanecarboxaldehyde (127 μL, 1.19 mmol) in CH_2Cl (2 mL) over 5 min. The mixture was stirred at -78 °C for 20 min and then at 0 °C for 1 h. Saturated aqueous NH_4Cl (~3 mL) was added followed by cold water (~2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 19:1) to provide 97 mg (40%) of **83** as a brown gum.

R_f = 0.73 (hexanes/EtOAc, 7:3); IR (neat): 2953, 2868, 2145, 1777, 1709, 1663, 1347, 1273, 1125, 1072, 1058, 1020, 960 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93 (d, 1H, J = 9.9 Hz, C_5H_9CH=C), 3.03-2.87 (m, 1H, CH_2CHCH_2), 2.00-7.86 (m, 2H, CH_2), 1.80-1.56

(m, 4H, CH_2), 1.47-1.32 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (*C*=O), 160.3 (O*C*=O), 143.2 (O-*C*=CHC$_5$H$_9$), 121.2 (C$_5$H$_9$*C*H=C), 36.8 (CH$_2$*C*HCH$_2$), 33.1 (2 × *C*H$_2$), 25.4 (2 × *C*H$_2$); HRMS (ESI, neg.): *m/z* 178.0628 (178.0630 calc. for $C_{10}H_{10}O_3$, $(M-N_2)^-$) and 223.0613 (223.0606 calc. for $C_{11}H_{11}O_5$, $(M+HCOO-N_2)^-$).

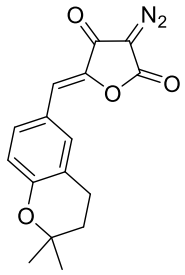
(*Z*)-3-Diazo-5-(naphthalen-2-ylmethylene)furan-2,4(3*H*,5*H*)-dione (84):



The reaction of **72** (150 mg, 1.19 mmol), 2-naphthaldehyde (186 mg, 1.19 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5 to 1:1), 292 mg (93%) of **84** as an orange-yellow solid.

R_f = 0.40 (hexanes/EtOAc, 7:3); mp: 156-160 °C; IR (neat): 2922, 2134, 1762, 1710, 1645, 1358, 1322, 1078, 1048, 976, 929 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H, Ar*H*), 7.94-7.80 (m, 4H, Ar*H*), 7.59-7.49 (m, 2H, Ar*H*), 6.86 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.4 (O*C*=O), 142.2 (O-*C*=CHAr), 134.0 (ArC_{ipso}), 133.3 (ArC_{ipso}), 132.6 (Ar*C*), 129.0 (Ar*C*), 128.9 (Ar*C*), 128.6 (ArC_{ipso}), 128.0 (Ar*C*), 127.9 (Ar*C*), 127.4 (Ar*C*), 126.9 (Ar*C*), 112.2 (Ar*C*H=C); HRMS (APPI, pos): *m/z* 264.0539 (264.0535 calc for $C_{15}H_8N_2O_3$ $(M)^+$).

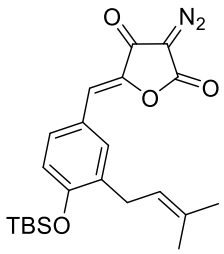
(*Z*)-3-Diazo-5-((2,2-dimethylchroman-6-yl)methylene)furan-2,4(3*H*,5*H*)-dione (85):



The reaction of **72** (200 mg, 1.59 mmol), 2,2-dimethylchroman-6-carbaldehyde (302 mg, 1.59 mmol), $TiCl_4$ (0.52 mL, 4.8 mmol) and 2,4,6-collidine (0.63 mL, 4.8 mmol) in CH_2Cl_2 (9 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 7:3), 430 mg (91%) of **85** as a yellow-orange solid.

R_f = 0.46 (hexanes/EtOAc, 7:3); mp: 156-161 °C; IR (neat): 2979, 2926, 2163, 1774, 1702, 1641, 1598, 1570, 1490, 1364, 1308, 1269, 1116, 1074, 1054, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1H, Ar*H*), 7.50 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.81 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.64 (s, 1H, ArC*H*=C), 2.81 (t, 2H, *J* = 6.7 Hz, ArC$H_2$$CH_2$), 1.83 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.36 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 160.6 (O*C*=O), 156.6 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 133.3 (Ar*C*), 131.4 (Ar*C*), 122.6 (ArC_{ipso}), 121.7 (ArC_{ipso}), 118.1 (Ar*C*), 112.7 (Ar*C*H=C), 75.5 (Ar-O-*C*$(CH_3)_2$), 32.5 (Ar*C*$H_2$$CH_2$), 26.9 (2 × *C*$H_3$), 22.4 (Ar$CH_2$*C*$H_2$); HRMS (ESI, pos.): *m/z* 298.0939 (298.0954 calc. for $C_{16}H_{14}N_2O_4$, $(M)^+$), 299.1012 (299.1032 calc. for $C_{16}H_{15}N_2O_4$, $(M+H)^+$) and 321.0827 (321.0851 calc. for $C_{16}H_{14}N_2NaO_4$, $(M+Na)^+$).

(*Z*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (86):



The reaction of **72** (350 mg, 2.78 mmol), 4-((tert-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (**109**) (846 mg, 2.78 mmol), $TiCl_4$ (0.90 mL, 8.3 mmol) and 2,4,6-collidine (1.10 mL, 8.33 mmol) in CH_2Cl_2 (12 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 19:1), 902 mg (79%) of **86** as a yellow solid.

R_f = 0.63 (hexanes/EtOAc, 7:3); mp: 118-121 °C; IR (neat): 2961, 2929, 2858, 2137, 1782, 1708, 1648, 1598, 1497, 1364, 1276, 1076, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, 1H, *J* = 8.4, 2.3 Hz, Ar*H*), 7.49 (d, 1H, *J* = 2.3 Hz, Ar*H*), 6.82 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 5.24-5.33 (m, 1H, $(CH_3)_2C$=C*H*), 3.30 (d, 2H, *J* = 7.1 Hz, C=CHCH_2), 1.77 (br d, 3H, *J* = 1.0 Hz, CH_3), 1.71 (br s, 3H, CH_3), 1.02 (s, 9H, 3 × CH_3), 0.27 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.4 (O*C*=O), 156.0 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 133.61 (Ar*C*), 133.57 (ArC_{ipso} or $(CH_3)_2C$=CH), 133.1 (ArC_{ipso} or $(CH_3)_2C$=CH), 130.6 (Ar*C* or $(CH_3)_2C$=*C*H), 123.9 (ArC_{ipso} or $(CH_3)_2C$=CH), 121.7 (Ar*C* or Ar*C*H=C), 118.9 (Ar*C* or Ar*C*H=C), 112.6 (Ar*C* or Ar*C*H=C), 28.4 (CH_2), 25.7 (4 × CH_3), 18.3 (Si-*C*$(CH_3)_3$), 17.9 (CH_3), -4.1 (2 × SiCH_3); HRMS (APPI, pos.): *m/z*

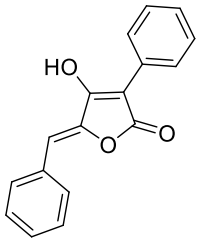
412.1827 (412.1818 calc. for $C_{22}H_{28}N_2O_4Si$, $(M)^+$) and 413.1859 (413.1897 calc. for $C_{22}H_{29}N_2O_4Si$, $(M+H)^+$).

General procedures for the insertion reactions of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones and arenes:

Method A: To a solution of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (1 equiv) in the aromatic compound was added the Rh(II) catalyst (1 mol%) at room temperature. The reaction mixture was then placed in a pre-heated oil bath at 100 °C. The mixture was heated until complete consumption of the diazo compound (TLC), then cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel.

Method B: To a suspension of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (1 equiv) in α,α,α-trifluorotoluene was added the aromatic compound (4 equiv) followed by the Rh(II) catalyst (1 mol%) at room temperature and the reaction mixture was placed in an oil bath that was pre-heated to 50 °C or to 100 °C. The mixture was heated until complete consumption of the diazo compound (TLC), then cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel.

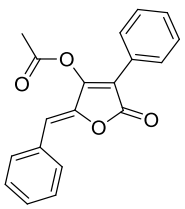
(*Z*)-5-Benzylidene-4-hydroxy-3-phenylfuran-2(5*H*)-one (1, Pulvinone):[5]



The reaction of **81** (40 mg, 0.19 mmol), $Rh_2(OAc)_4$ (0.80 mg, 1.9 x 10^{-3} mmol) in benzene (1.5 mL) at reflux for 42 h according to Method A provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3 to 1:1), 38 mg (78%, 81% based on recovery of **81**) of **1** as a yellow solid.

R_f = 0.17 (hexanes/EtOAc, 7:3); mp: 247-251 °C (Lit.[5] 250-251 ºC); IR (neat): 3007 (br), 2920, 2851, 2632 (br), 1698, 1621, 1595, 1406, 1332, 1303, 1210, 1150, 1122, 1001 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.98-7.91 (m, 2H, Ar*H*), 7.80-7.72 (m, 2H, Ar*H*), 7.53-7.27 (m, 6H, Ar*H*), 6.75 (s, 1H, PhC*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9 (*C*=O or C=*C*OH), 163.8 (*C*=O or C=*C*OH), 142.4 (O-*C*=CHPh), 132.7 (ArC_{ipso}), 130.1 (2 × Ar*C*), 129.8 (ArC_{ipso}), 129.0 (2 × Ar*C*), 128.8 (Ar*C*), 128.3 (2 × Ar*C*), 127.2 (2 × Ar*C*), 127.1 (Ar*C*), 107.6 (Ph*C*H=C), 100.1 (*C*=COH); HRMS (APPI, pos.): *m/z* 264.0796 (264.0786 calc. for $C_{17}H_{12}O_3$, $(M)^+$) and 265.0868 (265.0865 calc. for $C_{17}H_{13}O_3$, $(M+H)^+$).

(*Z*)-2-Benzylidene-5-oxo-4-phenyl-2,5-dihydrofuran-3-yl acetate (87):[5]

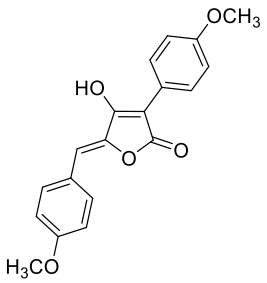


To a solution of pulvinone **1** (24 mg, 0.090 mmol) in pyridine (0.5 mL) was added acetic anhydride (0.2 mL) at room temperature and the mixture was stirred for 19 h. Water (2 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 4:1) to provide 9 mg (33%) of **87** as a yellow solid.

R_f = 0.51 (hexanes/EtOAc, 3:2); mp: 126-130 °C (Lit.[5] 138-140 ºC); IR (neat): 2956, 2922, 2852, 1785, 1761, 1614, 1492, 1446, 1370, 1286, 1167, 1134, 1093, 1065, 967, 921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83-7.72 (m, 4H, Ar*H*), 7.49-7.31 (m, 6H, Ar*H*), 6.08 (s, 1H, PhC*H*=C), 2.42 (s, 1H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5 (*C*(O)O), 165.7 (*C*(O)O), 154.6 (C=*C*OAc), 141.9 (O-*C*=CHPh), 132.3 (ArC_{ipso}), 130.8 (2 × Ar*C*), 129.5 (2 × Ar*C*), 128.9 (2 × Ar*C*), 128.8 (2 × Ar*C*), 127.9 (2 × Ar*C*, ArC_{ipso}), 115.9 (*C*=COAc), 109.6 (Ph*C*H=C), 20.8 (*C*H$_3$); HRMS (APPI, pos.): *m/z* 306.0904 (306.0892 calc. for $C_{19}H_{14}O_4$ $(M)^+$) and 307.0976 (307.0970 calc. for $C_{19}H_{15}O_4$, $(M+H)^+$).

^1H-^1H correlation spectroscopy does not show interaction between C*H*$_3$C(O)O- and PhC*H*=C.

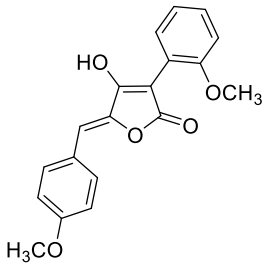
(*Z*)-4-Hydroxy-5-(4-methoxybenzylidene)-3-(4-methoxyphenyl)furan-2(5*H*)-one (88):[2]



The reaction of **76** (60 mg, 0.25 mmol), anisole (107 µL, 0.980 mmol), $Rh_2(CF_3CO_2)_4$ (1.6 mg, 2.5 x 10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) at 100 °C for 6 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 3:7), 56 mg (71%) of **88** as a brown solid and 16 mg (20%) of **89** as a yellow solid.

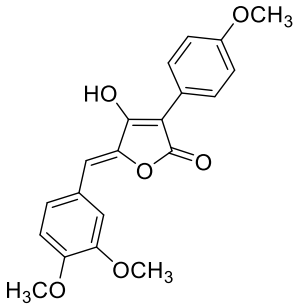
R_f = 0.21 (hexanes/EtOAc, 1:1); mp: 241-244 °C (Lit.[5] 250-253 ºC); IR (neat): 3003, 2954, 2833, 2601 (br), 1685, 1595, 1507, 1426, 1398, 1247, 1175, 1156, 1130, 1098, 1027, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/one drop DMSO-d_6): δ 7.90 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.71 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.91 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.87 (d, 2H, *J* = 8.9 Hz, Ar*H*), 6.47 (s, 1H, ArC*H*=C), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$/one drop DMSO-d_6): δ 169.0 (*C*=O or C=*C*OH), 162.3 (*C*=O or C=*C*OH), 159.7 (ArC_{ipso}), 158.4 (ArC_{ipso}), 141.1 (O-*C*=CHAr), 131.8 (2 × Ar*C*), 128.9 (2 × Ar*C*), 125.8 (ArC_{ipso}), 122.6 (ArC_{ipso}), 114.1 (2 × Ar*C*), 113.5 (2 × Ar*C*), 107.3 (Ar*C*H=C), 100.6 (*C*=COH), 55.2 (O*C*H_3), 55.1 (O*C*H_3); HRMS (APPI, pos.): *m/z* 324.0992 (324.0998 calc. for $C_{19}H_{16}O_5$, $(M)^+$) and 325.1064 (325.1076 calc. for $C_{19}H_{17}O_5$, $(M+H)^+$).

(*Z*)-4-Hydroxy-5-(4-methoxybenzylidene)-3-(2-methoxyphenyl)furan-2(5*H*)-one (89):



R_f = 0.40 (hexanes/EtOAc, 7:3); mp: 109-115 R °C; IR (neat): 2922 (br), 2838 (br), 1708, 1593, 1511, 1451, 1428, 1302, 1244, 1175, 1145, 1125, 1098, 1024, 983, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.12 (s, 1H, O*H*), 8.09 (dd, 1H, *J* = 7.8, 1.1 Hz, Ar*H*), 7.78 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.35 (ddd, 1H, *J* = 7.8, 7.5, 1.2 Hz, Ar*H*), 7.18 (br td, 1H, *J* = 7.8, 1.1 Hz, Ar*H*), 7.06 (dd, 1H, *J* = 8.2, 1.1 Hz, Ar*H*), 6.93 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.37 (s, 1H, ArC*H*=), 4.03 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (*C*=O or C=*C*OH), 162.8 (*C*=O or C=*C*OH or ArC_{ipso}), 160.3 (*C*=O or C=*C*OH or ArC_{ipso}), 154.7 (ArC_{ipso}), 140.3 (O-*C*=CHAr), 132.4 (2 × Ar*C*), 130.2 (Ar*C*), 129.3 (Ar*C*), 125.7 (ArC_{ipso}), 123.3 (Ar*C*), 119.4 (ArC_{ipso}), 114.4 (2 × Ar*C*), 113.0 (Ar*C*), 108.3 (Ar*C*H=C), 99.2 (*C*=COH), 57.7 (O*C*H_3), 55.5 (O*C*H_3); HRMS (APPI, pos.): *m/z* 324.0986 (324.0998 calc. for $C_{19}H_{16}O_5$, $(M)^+$) and 325.1058 (325.1076 calc. for $C_{19}H_{17}O_5$, $(M+H)^+$).

(*Z*)-5-(3,4-Dimethoxybenzylidene)-4-hydroxy-3-(4-methoxyphenyl)furan-2(5*H*)-one (90):[2]

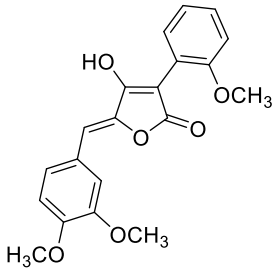


The reaction of **77** (90 mg, 0.33 mmol), anisole (142 µL, 1.31 mmol), $Rh_2(CF_3CO_2)_4$ (1.2 mg, 3.3 x 10^{-3} mmol) in α,α,α-trifluorotoluene (3 mL) at 100 °C for 22 h according to Method B provided, after purification by flash column chromatography on

silica gel (hexanes/EtOAc, 7:3 to 3:7), 61 mg (53%) of **90** as a brown solid and 16 mg (14%) of **91** as a yellow solid.

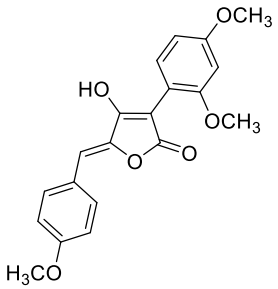
R_f = 0.22 (hexanes/EtOAc, 1:1); mp: 215-219 °C (Lit.[2] 219-222 °C); IR (neat): 3216 (br), 2959, 2921, 2851, 1693, 1657, 1625, 1595, 1510, 1464, 1443, 1425, 1401, 1242, 1139, 1096, 1018, 987 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$, 97:3): δ 7.81 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.45 (d, 1H, *J* = 1.7 Hz, Ar*H*), 7.30 (dd superimposed on $CHCl_3$ s, 1H, *J* = 8.2, 1.7 Hz, Ar*H*), 6.96 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.87 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.34 (s, 1H, ArC*H*=C), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1 (*C*=O or C=*C*OH), 162.7 (*C*=O or C=*C*OH), 158.1 (ArC_{ipso}), 149.6 (ArC_{ipso}), 148.7 (ArC_{ipso}), 141.0 (O-*C*=CHAr), 128.4 (2 × Ar*C*), 125.6 (ArC_{ipso}), 123.8 (Ar*C*), 122.4 (ArC_{ipso}), 113.8 (2 × Ar*C*), 113.0 (Ar*C*), 112.0 (Ar*C*), 107.3 (*C*=COH), 99.4 (Ar*C*H=C), 55.6 (O*C*H_3), 55.5 (O*C*H_3), 55.1 (O*C*H_3); HRMS (APPI, pos.): *m/z* 354.1116 (354.1103 calc. for $C_{20}H_{18}O_6$, $(M)^+$) and 355.1189 (355.1182 calc. for $C_{20}H_{19}O_6$, $(M+H)^+$).

(*Z*)-5-(3,4-Dimethoxybenzylidene)-4-hydroxy-3-(2-methoxyphenyl)furan-2(5*H*)-one (91):



R_f = 0.43 (hexanes/EtOAc, 1:1); mp: 104-108 °C; IR (neat): 3075 (br), 2954, 2923 (br), 2839, 1748, 1596, 1515, 1451, 1328, 1272, 1237, 1142, 1121, 1012, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (dd, 1H, *J* = 7.7, 1.7 Hz, Ar*H*), 7.45 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.40-7.32 (m, 2H, Ar*H*), 7.19 (td, 1H, *J* = 7.7, 1.1 Hz, Ar*H*), 7.07 (dd, 1H, *J* = 8.3, 1.1 Hz, Ar*H*), 6.89 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.35 (s, 1H, ArC*H*=C), 4.04 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3 (*C*=O or C=*C*OH), 162.8 (*C*=O or C=*C*OH), 154.7 (ArC_{ipso}), 150.1 (ArC_{ipso}), 149.2 (ArC_{ipso}), 140.5 (O-*C*=CHAr), 130.2 (Ar*C*), 129.4 (Ar*C*), 126.1 (ArC_{ipso}), 124.6 (Ar*C*), 123.3 (Ar*C*), 119.4 (ArC_{ipso}), 113.0 (2 × Ar*C*), 111.2 (Ar*C or* Ar*C*H=), 108.4 (Ar*C* or Ar*C*H=C), 99.2 (*C*=COH), 57.7 (O*C*H_3), 56.2 (O*C*H_3), 56.1 (O*C*H_3); HRMS (APPI, pos.): *m/z* 354.1100 (354.1103 calc. for $C_{20}H_{18}O_6$, $(M)^+$) and 355.1173 (355.1182 calc. for $C_{20}H_{19}O_6$, $(M+H)^+$).

(*Z*)-3-(2,4-Dimethoxyphenyl)-4-hydroxy-5-(4-methoxybenzylidene)furan-2(5*H*)-one (92):[2]



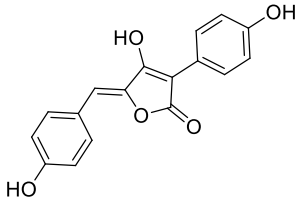
The reaction of **76** (65 mg, 0.27 mmol), 1,3-dimethoxybenzene (139 µL, 1.06 mmol), $Rh_2(CF_3CO_2)_4$ (1.7 mg, 2.7 x 10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) at 100 °C for 22 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3), 72 mg (76%) of **92** as a yellow solid.

R_f = 0.19 (hexanes/EtOAc, 7:3); mp: 176-178 °C (Lit.[2] 180-183 °C); IR (neat): 3258 (br), 2926 (br), 2841, 1751, 1603, 1577, 1508, 1327, 1299, 1253, 1210, 1160, 1096, 1023, 963, 932 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H, O*H*), 8.01 (d, 1H, *J* = 8.7 Hz, Ar*H*), 7.76 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.92 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.70 (dd, 1H, *J* = 8.7, 2.4 Hz, Ar*H*), 6.59 (d, 1H, *J* = 2.4 Hz, Ar*H*), 6.31 (s, 1H, ArC*H*=C), 4.00 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6 (*C*=O or C=*C*OH), 161.3 (*C*=O or C=*C*OH or ArC_{ipso}), 160.7 (*C*=O or C=*C*OH or ArC_{ipso}), 160.1 (*C*=O or C=*C*OH or ArC_{ipso}), 155.8 (ArC_{ipso}), 140.3 (O-*C*=CHAr), 132.1 (2 × Ar*C*), 130.8 (Ar*C*), 125.7 (ArC_{ipso}), 114.3 (2 × Ar*C*), 111.7 (ArC_{ipso}), 107.5 (Ar*C*), 107.1 (Ar*C*), 100.3 (Ar*C*H=C), 99.0 (*C*=COH), 57.3 (O*C*H_3), 55.6 (O*C*H_3), 55.3 (O*C*H_3); HRMS (APPI, pos.): *m/z* 354.1108 (354.1103 calc. for $C_{20}H_{18}O_6$, $(M)^+$) and 355.1181 (355.1182 calc. for $C_{20}H_{19}O_6$, $(M+H)^+$).

General procedure for the demethylation of aryl methyl ethers 88, 90 and 22:

To a solution of methoxypulvinones in CH_2Cl_2 was added BBr_3 (1M in CH_2Cl_2) at 0 °C. The mixture was warmed to room temperature, stirred for 20 min and then heated to reflux until consumption of the starting material (TLC). The mixture was then cooled to 0 °C and water (3 mL) was added. The resulting suspension was extracted with ethyl acetate (5 x 4 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was dissolved in dichloromethane with the aid of methanol and a few drops of hexanes were added. The mixture was left for a day at room temperature and the precipitated product (yellow solid) was isolated by filtration. This material was pure by ^1H NMR.

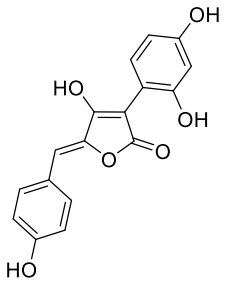
(*Z*)-4-Hydroxy-5-(4-hydroxybenzylidene)-3-(4-hydroxyphenyl)furan-2(5*H*)-one (2, Aspulvinone E):[2]



The reaction of **88** (80 mg, 0.25 mmol), BBr_3 (1.5 mL 1.5 mmol, 1.0 M in CH_2Cl_2) in dichloromethane (3 mL) for 3 h, according to the general procedure, provided 61 mg (84%) of **2** as a brown solid.

R_f = 0.27 (EtOAc/hexanes, 3:2); mp: 261-266 °C (Lit.[2] >250 °C); IR (neat): 3202 (br), 2923, 2853, 1695, 1602, 1509, 1443, 1408, 1340, 1248, 1194, 1158 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 7.74 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.65 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.82 (d, 4H, *J* = 8.7 Hz, Ar*H*), 6.40 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, CD_3OD): δ 171.2 (*C*=O or C=*C*OH), 163.3 (*C*=O or C=*C*OH), 159.7 (ArC_{ipso}), 157.9 (ArC_{ipso}), 141.8 (O-*C*=CHAr), 133.3 (2 × Ar*C*), 130.3 (2 × Ar*C*), 125.9 (ArC_{ipso}), 122.3 (ArC_{ipso}), 116.8 (2 × Ar*C*), 116.1 (2 × Ar*C*), 108.9 (Ar*C*H=C), 102.5 (*C*=COH); HRMS (APPI, pos.): *m/z* 296.0690 (296.0685 calc. for $C_{17}H_{12}O_5$, $(M)^+$) and 297.0763 (297.0763 calc. for $C_{17}H_{13}O_6$, $(M+H)^+$).

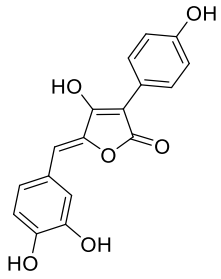
(*Z*)-3-(2,4-Dihydroxyphenyl)-4-hydroxy-5-(4-hydroxybenzylidene)furan-2(5*H*)-one (3, Aspulvinone G):[2]



The reaction of **92** (60 mg, 0.17 mmol), BBr_3 (1.5 mL, 1.5 mmol, 1.0 M in CH_2Cl_2) in dichloromethane (3 mL) for 2 h, according to the general procedure, provided 43 mg (81%) of **3** as a yellow solid.

R_f = 0.25 (EtOAc/hexanes, 3:2); mp: 243-248 °C (Lit.[2] >250 °C); IR (neat): 3151 (br), 1729, 1603, 1513, 1464, 1443, 1376, 1343, 1307, 1256, 1226, 1174, 1118, 1093, 983 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 7.64 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.60 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.82 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.43 (dd, 1H, *J* = 8.2, 2.1 Hz, Ar*H*), 6.42 (s, 1H, Ar*H*), 6.32 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, CD_3OD): δ 171.4 (*C*=O or C=*C*OH), 163.6 (*C*=O or C=*C*OH), 159.9 (ArC_{ipso}), 159.7 (ArC_{ipso}), 155.7 (ArC_{ipso}), 141.8 (O-*C*=CHAr), 133.3 (2 × Ar*C*), 131.7 (Ar*C*), 126.1 (ArC_{ipso}), 116.8 (2 × Ar*C*), 109.6 (ArC_{ipso}), 109.1 (Ar*C*), 108.5 (Ar*C*), 103.9 (Ar*C*H=C), 100.1 (*C*=COH); HRMS (APPI, pos.): *m/z* 312.0635 (312.0634 calc. for $C_{17}H_{12}O_6$, $(M)^+$) and 313.0708 (313.0712 calc. for $C_{17}H_{13}O_6$, $(M+H)^+$).

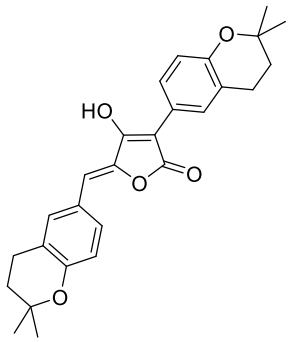
(*Z*)-5-(3,4-Dihydroxybenzylidene)-4-hydroxy-3-(4-hydroxyphenyl)furan-2(5*H*)-one (3',4,'4-Trihydroxypulvinone (4)):[7]



The reaction of **90** (55 mg, 0.16 mmol), BBr_3 (1.6 mL, 1.6 mmol, 1.0 M in CH_2Cl_2) in dichloromethane (2 mL) for 4 h, according to general procedure, provided 41 mg (85%) of **4** as a brown solid.

R_f = 0.31 (EtOAc/hexanes, 3:2); mp: 277-283 °C (Lit.[7] 289-291 °C); IR (neat): 3304 (br), 2921, 2628 (br), 1693, 1597, 1509, 1443, 1407, 1326, 1241, 1156, 1129, 1098, 1015, 964 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 10.43 (br s, 1H, O*H*), 8.51 (s, 1H, O*H*), 8.36 (s, 1H, O*H*), 8.24 (s, 1H, O*H*), 7.83 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.47 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.09 (dd, 1H, *J* = 8.2, 2.0 Hz, Ar*H*), 6.89 (d, 1H, *J* = 8.8 Hz, Ar*H*), 6.87 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.44 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, CD_3OD): δ 171.4 (*C*=O or C=*C*OH), 163.4 (*C*=O or C=*C*OH), 158.0 (ArC_{ipso}), 148.2 (ArC_{ipso}), 146.7 (ArC_{ipso}), 141.8 (O-*C*=CHAr), 130.3 (2 × Ar*C*), 126.4 (ArC_{ipso}), 124.9 (Ar*C*), 122.4 (ArC_{ipso}), 118.0 (Ar*C*), 116.5 (Ar*C*), 116.1 (2 × Ar*C*), 109.4 (Ar*C*H=C), 102.5 (*C*=COH); HRMS (APPI, pos.): *m/z* 312.0628 (312.0634 calc. for $C_{17}H_{12}O_6$, $(M)^+$) and 313.0704 (313.0712 calc. for $C_{17}H_{13}O_6$, $(M+H)^+$).

(*Z*)-3-(2,2-Dimethylchroman-6-yl)-5-((2,2-dimethylchroman-6-yl)methylene)-4-hydroxyfuran-2(5*H*)-one (5, Aspulvinone A):[2,15]

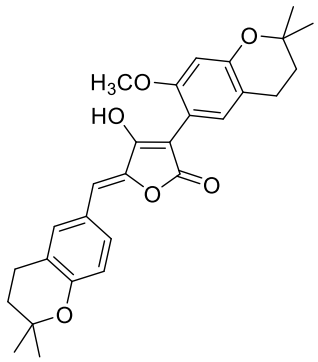


The reaction of **85** (60 mg, 0.21 mmol), 2,2-dimethylchroman (134 mg, 0.830 mmol), $Rh_2(esp)_2$ (1.6 mg, 2.1 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 50 °C for 6 h according to Method B provided, after purification by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 9.8:0.2 to 9:1), 63 mg (60%) of **5** as a yellow solid.

R_f = 0.12 (hexanes/EtOAc, 7:3); mp: 244-247 °C (Lit.[2] 241-243 °C); IR (neat): 2973 (br), 2928 (br), 1690, 1624, 1605, 1572, 1495, 1390, 1300, 1259, 1234, 1154, 1121, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6, 95:5): δ 10.99 (br, 1H, O*H*), 7.70 (s, 1H, Ar*H*), 7.68 (dd, 1H, *J* = 8.6. 2.0 Hz, Ar*H*), 7.56 (br d, 1H, *J* = 2.0 Hz, Ar*H*), 7.48 (dd, 1H, *J* = 8.6. 2.0 Hz, Ar*H*), 6.79 (dd, 1H, *J* = 8.6. 2.0 Hz, Ar*H*), 6.76 (d, 1H, *J* = 8.6 Hz, Ar*H*), 6.47 (s, 1H, ArC*H*=C), 2.83 (br t, 2H, *J* = 6.7 Hz, ArC$H_2$$CH_2$), 2.82 (br t, 2H, *J* = 6.7 Hz, ArC$H_2$$CH_2$), 1.83 (t, 2H, *J* = 6.7 Hz, Ar$CH_2$$CH_2$), 1.82 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.35 (s, 6H, 2 × CH_3), 1.34 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1 (*C*=O or C=*C*OH), 162.0 (*C*=O or C=*C*OH), 154.5 (ArC_{ipso}), 152.8 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 131.6 (Ar*C*), 129.6 (Ar*C*), 128.4 (Ar*C*), 126.4 (Ar*C*), 124.4 (ArC_{ipso}), 121.5 (ArC_{ipso}), 121.3

(ArC_{ipso}), 120.6 (ArC_{ipso}), 117.5 (Ar*C*), 116.6 (Ar*C*), 107.3 (O-C=*C*HAr), 99.7 (*C*=COH), 74.9 (Ar-O-*C*$(CH_3)_2$), 74.3 (Ar-O-*C*$(CH_3)_2$), 32.1 (Ar*C*H_2CH_2), 31.9 (Ar*C*H_2CH_2), 26.6 (4 × *C*H_3), 22.0 (ArCH_2*C*H_2), 21.8 (ArCH_2*C*H_2); HRMS (APPI, pos.): *m/z* 432.1921 (432.1937 calc for $C_{27}H_{28}O_5$ $(M)^+$) and 433.1993 (433.2015 calc for $C_{27}H_{29}O_5$ $(M+H)^+$).

(*Z*)-5-((2,2-Dimethylchroman-6-yl)methylene)-4-hydroxy-3-(7-methoxy-2,2-dimethylchroman-6-yl)furan-2(5*H*)-one (95):

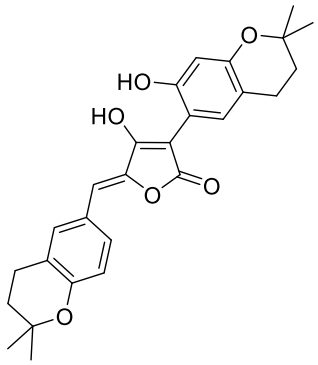


The reaction of **85** (60 mg, 0.20 mmol), 7-methoxy-2,2-dimethylchroman (**94**) (155 mg, 0.800 mmol), $Rh_2(esp)_2$ (1.30 mg, 2.01 x 10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) at 50 °C for 2 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 8.5:1.5), 79 mg (85%) of **95** as a yellow solid.

R_f = 0.26 (hexanes/EtOAc, 9.5:0.5); mp: 200-204 °C; IR (neat): 3277 (br), 2976, 2933 (br), 2848, 1742, 1605, 1578, 1492, 1451, 1309, 1260, 1151, 1117, 1089, 1017, 976, 945 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (s, 1H, O*H*), 7.78 (s, 1H, Ar*H*), 7.60 (br d, 1H, *J* = 1.8 Hz, Ar*H*), 7.51 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar*H*), 6.79 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.49 (s, 1H, Ar*H*), 6.27 (s, 1H, ArC*H*=C), 3.96 (s, 3H, OCH_3), 2.82 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2),

2.80 (t, 2H, J = 6.7 Hz, ArCH_2CH_2) (overlapping triplets), 1.83 (t, 2H, J = 6.7 Hz, ArCH_2CH_2), 1.82 (t, 2H, J = 6.7 Hz, ArCH_2CH_2), 1.35 (s, 12H, 4 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (*C*=O or C=*C*OH), 161.3 (*C*=O or C=*C*OH), 155.0 (ArC_{ipso}), 154.9 (ArC_{ipso}), 154.2 (ArC_{ipso}), 139.9 (O-*C*=CHAr), 131.9 (Ar*C*), 130.5 (Ar*C*), 130.2 (Ar*C*), 124.8 (ArC_{ipso}), 121.3 (ArC_{ipso}), 117.7 (Ar*C*), 115.5 (ArC_{ipso}), 110.7 (ArC_{ipso}), 107.8 (Ar*C*), 101.6 (Ar*C*H=C), 99.0 (*C*=COH), 75.2 (Ar-O-*C*$(CH_3)_2$), 75.0 (Ar-O-*C*$(CH_3)_2$), 57.3 (O*C*H_3), 32.8 (Ar*C*H_2CH_2), 32.7 (Ar*C*H_2CH_2), 26.94 (2 × *C*H_3), 26.86 (2 × *C*H_3), 22.5 (ArCH_2*C*H_2), 21.8 (ArCH_2*C*H_2); HRMS (APPI, pos.): *m/z* 462.2042 (462.2042 calc. for $C_{28}H_{30}O_6$, $(M)^+$) and 463.2114 (463.2121 calc. for $C_{28}H_{31}O_6$, $(M+H)^+$).

(*Z*)-5-((2,2-Dimethylchroman-6-yl)methylene)-4-hydroxy-3-(7-hydroxy-2,2-dimethylchroman-6-yl)furan-2(5*H*)-one (6, Aspulvinone C):[15,16]

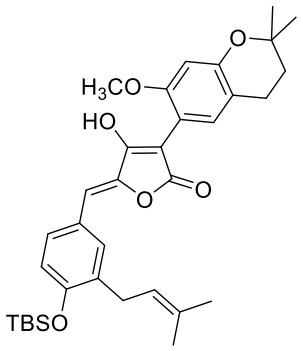


To a solution of compound **95** (50 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (0.32 mL, 0.32 mmol, 1.0 M in CH_2Cl_2) at -78 °C and the mixture was stirred for 40 min. The reaction mixture was then warmed to 0 °C and stirred for 20 min. Water (2 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 4 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved

in dichloromethane (3 mL), a few drops of hexanes were added, and the mixture was allowed to stand at room temperature for 22 h to provide 36 mg (75%) of **6** (Aspulvinone C) as a yellow solid that was isolated by filtration. This was pure by ^{1}H NMR.

R_f = 0.61 (EtOAc/hexanes, 7:3); mp: 224-230 °C; IR (neat): 3065 (br), 2973, 2924 (br), 1709, 1602, 1494, 1428, 1343, 1284, 1263, 1229, 1154, 1109, 1088 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 (s, 1H, Ar*H*), 7.48 (dd, 1H, *J* = 8.9, 2.1 Hz, Ar*H*), 7.11 (s, 1H, Ar*H*), 6.77 (d, 1H, *J* = 8.9 Hz, Ar*H*), 6.28 (s, 1H, Ar*H* or ArC*H*=C), 6.24 (s, 1H, Ar*H* or ArC*H*=C), 2.78 (t, 2H, *J* = 6.6 Hz, ArCH_2CH$_2$), 2.64 (t, 2H, *J* = 6.6 Hz, ArCH_2CH$_2$), 1.79 (t, 2H, *J* = 6.6 Hz, ArCH$_2$CH_2), 1.73 (t, 2H, *J* = 6.6 Hz, ArCH_2CH_2), 1.30 (s, 6H, 2 × CH_3), 1.27 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or C=*C*OH), 163.6 (*C*=O or C=*C*OH), 154.20 (Ar*C*$_{ipso}$), 154.19 (Ar*C*$_{ipso}$), 154.1 (Ar*C*$_{ipso}$), 141.3 (O-*C*=CHAr), 131.4 (Ar*C*), 130.6 (Ar*C*), 129.4 (Ar*C*), 124.7 (Ar*C*$_{ipso}$), 121.3 (Ar*C*$_{ipso}$), 117.3 (Ar*C*), 111.5 (Ar*C*$_{ipso}$), 108.8 (Ar*C*$_{ipso}$), 105.5 (Ar*C* *or* Ar*C*H=C), 103.4 (Ar*C* *or* Ar*C*H=C), 97.9 (*C*=COH), 74.8 (Ar-O-*C*(CH$_3$)$_2$), 74.1 (Ar-O-*C*(CH$_3$)$_2$), 32.4 (Ar*C*H$_2$CH$_2$), 32.0 (Ar*C*H$_2$CH$_2$), 26.62 (2 × *C*H$_3$), 26.59 (2 × *C*H$_3$), 21.8 (ArCH$_2$*C*H$_2$), 21.2 (ArCH$_2$*C*H$_2$); HRMS (ESI, pos.): *m/z* 448.1866 (448.1886 calc for $C_{27}H_{28}O_6$ $(M)^+$) and 471.1755 (471.1784 calc for $C_{27}H_{28}NaO_6$ $(M+Na)^+$).

(*Z*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzylidene)-4-hydroxy-3-(7-methoxy-2,2-dimethylchroman-6-yl)furan-2(5*H*)-one (97):

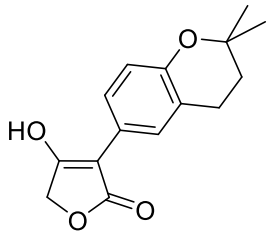


The reaction of **86** (100 mg, 0.240 mmol), 7-methoxy-2,2-dimethylchroman (**94**) (186 mg, 0.970 mmol), $Rh_2(esp)_2$ (1.6 mg, 2.4 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2.5 mL) at 50 °C for 4 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9.5:0.5 to 9:1), 61 mg (44%) of **97** as a yellow solid.

R_f = 0.29 (hexanes/EtOAc, 3:2); mp: 67-72 °C; IR (neat): 2953 (br), 2928 (br), 2855, 1749, 1601, 1495, 1466, 1326, 1255, 1153, 1118, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H, Ar*H*), 7.66 (dd, 1H, *J* = 8.4, 2.3 Hz, Ar*H*), 7.47 (d, 1H, *J* = 2.3 Hz, Ar*H*), 6.81 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.49 (s, 1H, Ar*H* or ArC*H*=C), 6.28 (s, 1H, Ar*H* or ArC*H*=C), 5.32-5.26 (m, 1H, $(CH_3)_2C$=C*H*), 3.95 (s, 3H, OCH_3), 3.32 (d, 1H, *J* = 7.1 Hz, CH_2CH=CH_2), 2.79 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.81 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.77 (d, 3H, *J* = 1.3 Hz, CH_3), 1.72 (s, 3H, CH_3), 1.35 (s, 6H, 2 × CH_3), 1.02 (s, 9H, C(CH_3)$_3$), 0.26 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (*C*=O or C=*C*OH), 161.2 (*C*=O or C=*C*OH), 154.9 (ArC_{ipso}), 154.3 (ArC_{ipso}), 154.2 (ArC_{ipso}), 140.3 (O-*C*=CHAr), 133.0

(ArC_{ipso} or $(CH_3)_2C$=C), 132.6 (ArC_{ipso} or $(CH_3)_2C$=C), 132.3 (Ar*C*), 130.5 (Ar*C*), 129.3 (Ar*C*), 126.1 (ArC_{ipso} or $(CH_3)_2C$=C), 122.3 (Ar*C* or $(CH_3)_2$C=*C*H), 118.8 (Ar*C* or $(CH_3)_2$C=*C*H), 115.5 (ArC_{ipso}), 110.7 (ArC_{ipso}), 107.8 (Ar*C* or Ar-*C*H), 101.7 (Ar*C* or Ar*C*H=C), 99.2 (*C*=COH), 75.2 (Ar-O-*C*$(CH_3)_2$), 57.3 (O*C*H_3), 32.8 (*C*H_2), 28.5 (*C*H_2), 26.9 (O-C(*C*$H_3)_2$), 25.8 (Si-C(*C*$H_3)_3$ and 1 × C=C(*C*$H_3)_2$), 21.8 (*C*H_2), 18.3 (Si-*C*$(CH_3)_3$), 17.9 (1 × C=C(*C*$H_3)_2$), –4.1 (Si(*C*$H_3)_2$); HRMS (APPI, pos.): *m/z* 576.2897 (576.2907 calc. for $C_{34}H_{44}O_6Si$, $(M)^+$) and 577.2969 (577.2985 calc. for $C_{34}H_{45}O_6Si$, $(M+H)^+$).

3-(2,2-Dimethylchroman-6-yl)-4-hydroxyfuran-2(5*H*)-one (102):

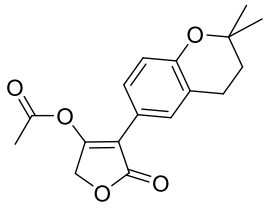


The reaction of **72** (100 mg, 0.790 mmol), 2,2-dimethylchroman (515 mg, 3.17 mmol), $Rh_2(esp)_2$ (6.0 mg, 7.9×10^{-3} mmol) in *α,α,α*-trifluorotoluene (2 mL) at 50 °C for 5 h according to Method B provided, after purification of the crude product by trituration with hexanes/dichloromethane (8:2), 157mg (76%) of **102** as a white solid.

R_f = 0.11 (hexanes/EtOAc, 3:2); mp: 213-217 °C; IR (neat): 2974, 2930, 2583 (br), 1696, 1585, 1498, 1438, 1381, 1346, 1327, 1261, 1219, 1154, 1122, 1064, 1024, 946 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.49 (br s, 1H, O*H*), 7.63 (br d, 1H, *J* = 2.1 Hz, Ar*H*), 7.60 (br dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.70 (d, 1H, *J* = 8.3 Hz, Ar*H*), 4.73 (s, 2H, OCH_2), 2.73 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.76 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.27 (s, 6H, 2× CH_3);

^{13}C NMR (75 MHz, DMSO-d_6): δ 173.1 (*C*=O or C=*C*OH), 172.9 (*C*=O or C=*C*OH), 152.1 (Ar*C*$_{ipso}$), 127.5 (Ar*C*), 125.6 (Ar*C*), 121.8 (Ar*C*$_{ipso}$), 120.3 (Ar*C*$_{ipso}$), 116.3 (Ar*C*), 97.4 (*C*=COH), 74.1 (Ar-O-*C*(CH$_3$)$_2$), 65.9 (O*C*H$_2$), 32.2 (*C*H$_2$), 26.6 (2 × *C*H$_3$), 22.0 (*C*H$_2$); HRMS (APPI, pos.): *m/z* 260.1052 (260.1049 calc. for $C_{15}H_{16}O_4$, $(M)^+$)

4-(2,2-Dimethylchroman-6-yl)-5-oxo-2,5-dihydrofuran-3-yl acetate (103):

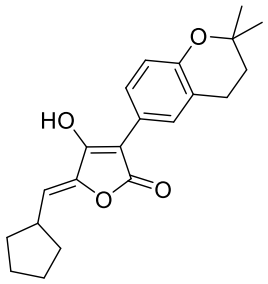


To a solution of tetronic acid **102** (150 mg, 0.580 mmol) in pyridine (2 mL) was added acetic anhydride (1 mL) over 5 min at room temperature and the mixture was stirred for 51 h. Water was added and the resulting mixture was extracted with dichloromethane (3 × 8 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc, 3:1) to provide 95 mg (55%) of **103** as a white solid.

R_f = 0.21 (hexanes/EtOAc, 3:1); mp: 152-156 °C; IR (neat): 2977, 2934, 2847, 1787, 1732, 1648, 1496, 1367, 1270, 1221, 1189, 1156, 1132, 1038, 1002, 981 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (br d, 1H, *J* = 2.2 Hz, Ar*H*), 7.51 (dd, 1H, *J* = 8.6, 2.2 Hz, Ar*H*), 6.82 (d, 1H, *J* = 8.6 Hz, Ar*H*), 5.22 (s, 2H, OC*H*$_2$), 2.82 (t, 2H, *J* = 6.7 Hz, ArC*H*$_2$CH$_2$), 2.36 (s, 3H, COC*H*$_3$), 1.82 (t, 2H, *J* = 6.7 Hz, ArCH$_2$C*H*$_2$), 1.35 (s, 6H, 2 × C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (*C*(O)O), 166.3 (*C*(O)O), 161.6 (Ar*C*$_{ipso}$ or CH$_3$C(O)O*C*=C), 154.6 (Ar*C*$_{ipso}$ or CH$_3$C(O)O*C*=C), 129.4 (Ar*C*), 127.4 (Ar*C*), 121.0 (Ar*C*$_{ipso}$), 119.1 (Ar*C*$_{ipso}$),

117.4 (Ar*C*), 110.6 ($CH_3C(O)OC=C$), 74.8 (Ar-O-$C(CH_3)_2$), 67.3 (OCH_2), 32.7 ($ArCH_2CH_2$), 26.9 (2 × CH_3), 22.5 ($ArCH_2CH_2$), 21.1 ($COCH_3$); HRMS (ESI, pos.): *m/z* 302.1155 (302.1154 calc. for $C_{17}H_{18}O_5$, $(M)^+$) and 325.1047 (325.1052 calc. for $C_{17}H_{18}NaO_5$, $(M+Na)^+$).

(*Z*)-5-(Cyclopentylmethylene)-3-(2,2-dimethylchroman-6-yl)-4-hydroxyfuran-2(5*H*)-one (105):

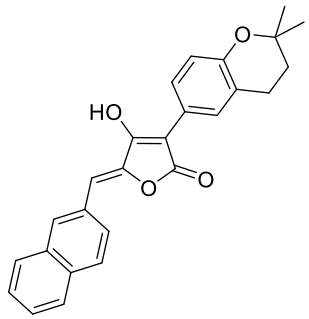


The reaction of **83** (56 mg, 0.27 mmol), 2,2-dimethylchroman (**93**) (176 mg, 1.08 mmol), $Rh_2(esp)_2$ (1.8 mg, 2.7 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 50 °C for 22 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 7:3), 54 mg (58%) of **105** as a white solid.

R_f = 0.21 (hexanes/EtOAc, 7:3); mp: 176-179 °C; IR (neat): 2942 (br), 2865 (br), 1697, 1670, 1627, 1613, 1576, 1497, 1438, 1395, 1370, 1253, 1223, 1155, 1120, 1099, 1003 cm^{-1}; ^1H NMR NMR (300 MHz, $CDCl_3/CD_3OD$, 95:5): δ 7.60 (br s, 1H, Ar*H*), 7.57 (dd, 1H, *J* = 8.3, 2.2 Hz, Ar*H*), 6.78 (d, 1H, *J* = 8.3, Hz, Ar*H*), 5.56 (d, 1H, *J* = 9.7 Hz, C_5H_9CH=C), 3.16-3.00 (m, 1H, CH_2CHCH_2), 2.81 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 2.02-1.87 (m, 2H, CH_2), 1.81 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.77-1.56 (m, 4H, CH_2), 1.48-1.24 (m, 2H, CH_2), 1.34 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$, 95:5): δ 169.9 (*C*=O or

C=*C*OH), 160.8 (*C*=O or C=*C*OH), 153.4 (Ar*C*$_{ipso}$), 142.9 (O-*C*=CHAr), 129.1 (Ar*C*), 127.2 (Ar*C*), 121.2 (Ar*C*$_{ipso}$), 121.0 (Ar*C*$_{ipso}$), 117.1 (Ar*C* or O-C=*C*HAr), 115.6 (Ar*C* or O-C=*C*HAr), 102.6 (*C*=COH), 74.7 (Ar-O-*C*(CH$_3$)$_2$), 37.1 (*C*H(CH$_2$)$_2$), 33.7 (2 × *C*H$_2$), 32.9 (*C*H$_2$), 26.9 (2 × *C*H$_3$), 25.4 (2 × *C*H$_2$), 22.5 (*C*H$_2$); HRMS (APPI, pos.): *m/z* 340.1667 (340.1675 calc. for $C_{21}H_{24}O_4$, $(M)^+$) and 341.1739 (341.1753 calc. for $C_{21}H_{25}O_4$, $(M+H)^+$).

(*Z*)-3-(2,2-Dimethylchroman-6-yl)-4-hydroxy-5-(naphthalen-2-ylmethylene)furan-2(5*H*)-one (106):

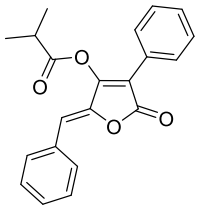


The reaction of **84** (70 mg, 0.27 mmol), 2,2-dimethylchroman (**93**) (175 mg, 1.08 mmol), Rh$_2$(esp)$_2$ (1.8 mg, 2.7 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 70 °C for 5 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 1:1), 44 mg (42%) of **106** as a yellow solid.

R_f = 0.15 (hexanes/EtOAc, 3:2); mp: 164-169 °C; IR (neat): 3053 (br), 2974 (br), 2929 (br) 2849, 1695, 1621, 1495, 1386, 1314, 1267, 1222, 1156, 1118, 1020, 943 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 8.20 (s, 1H, Ar*H*), 8.04-7.88 (m, 4H, Ar*H*), 7.70 (s, 1H, Ar*H*), 7.70-7.65 (br s, 1H, Ar*H*), 7.60-7.57 (m, 2H, Ar*H*), 6.83 (s, 1H, ArC*H*=C), 6.78 (d, 1H, *J* = 8.3 Hz, Ar*H*), 2.78 (t, 2H, *J* = 6.7 Hz, ArC*H*$_2$CH$_2$), 1.79 (t, 2H, *J* = 6.7 Hz, ArCH$_2$C*H*$_2$),

1.30 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1 (*C*=O or C=*C*OH), 162.2 (*C*=O or C=*C*OH), 152.9 (ArC_{ipso}), 142.9 (O-*C*=CHAr), 133.0 (ArC_{ipso}), 132.6 (ArC_{ipso}), 130.6 (ArC_{ipso}), 129.7 (Ar*C*), 128.5 (2 × Ar*C*), 128.3 (Ar*C*), 127.6 (Ar*C*), 127.0 (Ar*C*), 126.9 (Ar*C*), 126.7 (Ar*C*), 126.5 (Ar*C*), 121.2 (ArC_{ipso}), 120.6 (ArC_{ipso}), 116.7 (Ar*C*), 106.8 (O-C=*C*HAr), 100.3 (*C*=COH), 74.4 (Ar-O-*C*$(CH_3)_2$), 32.1 (Ar*C*H_2CH_2), 26.6 (2 × *C*H_3), 22.0 (ArCH_2*C*H_2); HRMS (APPI, pos.): *m/z* 398.1509 (398.1518 calc. for $C_{26}H_{22}O_4$, $(M)^+$) and 399.1580 (399.1596 calc. for $C_{26}H_{23}O_4$, $(M+H)^+$).

(*Z*)-2-Benzylidene-5-oxo-4-phenyl-2,5-dihydrofuran-3-yl isobutyrate (107):[5]



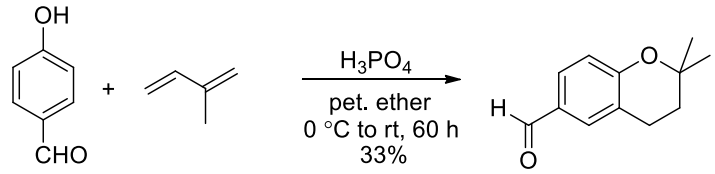
To a solution of pulvinone (**1)** (35 mg, 0.13 mmol) in dichloromethane (0.5 mL) were added DMAP (1.6 mg, 1.3 × 10^{-2} mmol) and diisopropylethylamine (25 µL, 0.15 mmol) followed by isobutyryl chloride (15 µL, 0.15 mmol) at 0 °C. The mixture was then stirred at room temperature for 4 h. Water (2 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 95:5) to provide 36 mg (82%) of **107** as a yellow solid.

R_f = 0.29 (hexanes/EtOAc, 9:1); mp: 125-129 °C (Lit.[5] 128-129); IR (neat): 2972, 2929, 1759, 1657, 1637, 1445, 1375, 1345, 1286, 1106, 1075, 1043, 966, 926 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83-7.69 (m, 4H, Ar*H*), 7.48-7.30 (m, 6H, Ar*H*), 6.01 (s, 1H, PhC*H*=C),

2.94 (septet, 1H, J = 6.9 Hz, CH(CH_3)$_2$), 1.37 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (*C*(O)O), 166.7 (*C*(O)O), 155.0 (C=*C*OC(O)CH(CH_3)$_2$), 142.2 (O-*C*=CHAr), 132.4 (ArC_{ipso}), 130.9 (2 × Ar*C*), 129.5 (2 × Ar*C*), 129.0 (2 × Ar*C*), 128.8 (2 × Ar*C*), 128.2 (2 × Ar*C*), 128.0 (ArC_{ipso}), 116.1 (Ph*C*=COC(O)CH(CH_3)$_2$), 109.5 (Ph*C*H=C), 34.4 (*C*H(CH_3)$_2$), 18.9 (2 × *C*H_3); HRMS (APPI, pos.): *m/z* 334.1205 (334.1205 calc. for $C_{21}H_{18}O_4$ $(M)^+$) and 335.1282 (335.1283 calc. for $C_{21}H_{19}O_4$, $(M+H)^+$).

^{1}H-^{1}H correlation spectroscopy does not show interaction between (CH_3)$_2$CHC(O)O- and PhC*H*=C.

2,2-Dimethylchromane-6-carbaldehyde (110)[17]

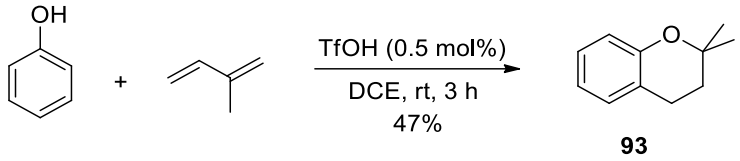


To a suspension of 4-hydroxybenzaldehyde (2.00 g, 16.4 mmol) in petroleum ether (25 mL) was added orthophosphoric acid (1.70 mL, 32.8 mmol) followed by isoprene (3.28 mL, 32.8 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 60 h. Cold water (25 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 93:7) to provide 1.04 g (33%) of 2,2-dimethylchromane-6-carbaldehyde (**110**) as a brown liquid.

R_f = 0.32 (hexanes/EtOAc, 4:1); IR (neat): 2976, 2920, 2828, 2796, 2737, 1672, 1606, 1572, 1492, 1328, 1267, 1236, 1155, 1119, 1104, 948 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):

δ 9.83 (s, 1H, C*H*O), 7.65-7.59 (m, 2H, Ar*H*), 6.86 (d, 1H, *J* = 8.9 Hz, Ar*H*), 2.84 (t, 2H, *J* = 6.7 Hz, ArC*H*$_2$CH$_2$), 1.85 (t, 2H, *J* = 6.7 Hz, ArCH$_2$C*H*$_2$), 1.37 (s, 6H, 2 × C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.0 (*C*HO), 159.8 (Ar*C*$_{ipso}$), 132.0 (Ar*C*), 129.6 (Ar*C*), 129.0 (Ar*C*$_{ipso}$), 121.4 (Ar*C*$_{ipso}$), 117.9 (Ar*C*), 75.9 (Ar-O-*C*(CH$_3$)$_2$), 32.4 (Ar*C*H$_2$CH$_2$), 26.9 (2 × *C*H$_3$), 22.2 (ArCH$_2$*C*H$_2$).

2,2-Dimethylchromane (93):[18]

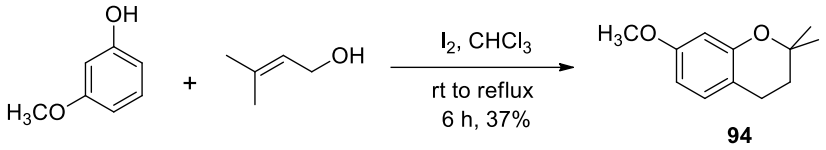


93

To a solution of phenol (1.00 g, 10.6 mmol) in dichloroethane (25 mL) was added isoprene (1.60 mL, 15.9 mmol) followed by triflic acid (5.0 µL, 5.3 × 10^{-2} mmol) at room temperature and the mixture was stirred for 3 h. The mixture was then concentrated and the residue was directly purified by flash column chromatography on silica gel (hexanes) to provide 647 mg (38%) of **93** as a colorless liquid.

R_f = 0.21 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2974, 2927, 1582, 1489, 1452, 1368, 1305, 1254, 1219, 1155, 1121, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.01 (m, 2H, Ar*H*), 6.82 (dd, 1H, *J* = 7.3, 1.2 Hz, Ar*H*), 6.77 (br d, 1H, *J* = 8.4 Hz, Ar*H*), 2.77 (t, 2H, *J* = 6.7 Hz, ArC*H*$_2$CH$_2$), 1.80 (t, 2H, *J* = 6.7 Hz, ArCH$_2$CH$_2$), 1.33 (s, 6H, 2 × C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (Ar*C*$_{ipso}$), 129.4 (Ar*C*), 127.2 (Ar*C*), 120.9 (Ar*C*$_{ipso}$), 119.6 (Ar*C*), 117.2 (Ar*C*), 74.1 (Ar-O-*C*(CH$_3$)$_2$), 32.8 (Ar*C*H$_2$CH$_2$), 26.9 (2 × *C*H$_3$), 22.5 (ArCH$_2$*C*H$_2$).

7-Methoxy-2,2-dimethylchromane (94):[19]

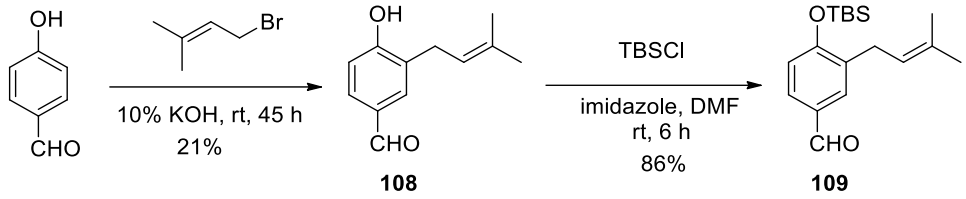


94

To a solution of prenyl alcohol (0.70 mL, 7.0 mmol) in chloroform (10 mL) was added 3-methoxyphenol (3.00 mL, 28.9 mmol) followed by iodine (530 mg, 2.09 mmol) at room temperature and the mixture was heated to reflux for 6 h, cooled to room temperature and then diluted with dichloromethane (25 mL). The resulting mixture was washed with aqueous $Na_2S_2O_3$ (5%, 2 × 15 mL) and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 99:1) to provide 496 mg (37%) of **94** as a colorless liquid.

R_f = 0.34 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2974, 2934 (br), 2850, 1620, 1585, 1503, 1467, 1441, 1269, 1246, 1199, 1149, 1119, 1092, 1037, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.42 (dd, 1H, *J* = 8.3, 2.5 Hz, Ar*H*), 6.34 (d, 1H, *J* = 2.5 Hz, Ar*H*), 3.74 (s, 3H, OCH_3), 2.70 (t, 2H, *J* = 6.7 Hz, ArCH_2CH$_2$), 1.78 (t, 2H, *J* = 6.7 Hz, ArCH$_2$CH_2), 1.33 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1 (ArC_{ipso}), 154.7 (ArC_{ipso}), 129.9 (Ar*C*), 113.0 (ArC_{ipso}), 106.9 (Ar*C*), 101.7 (Ar*C*), 74.3 (Ar-O-*C*(CH$_3$)$_2$), 55.2 (O*C*H$_3$), 33.0 (Ar*C*H$_2$CH$_2$), 26.8 (2 × *C*H$_3$), 21.7 (ArCH$_2$*C*H$_2$).

4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (109):[20]



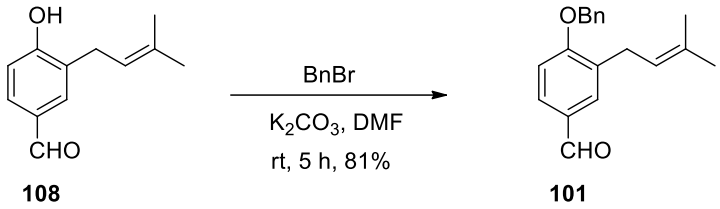
To a solution of 4-hydroxybenzaldehyde (3.20 g, 26.5 mmol) in 10% aqueous potassium hydroxide (15 mL) was added prenyl bromide (5.50 mL, 47.6 mmol) dropwise over 10 min at room temperature and the mixture was stirred for 45 h. The reaction mixture was then cooled to 0 °C and acidified to pH~3 with 2 N HCl. The resulting suspension was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 9:1) to provide, 1.04 g (21%) of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (**108**) as a pale-yellow liquid.

To a solution of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (**108**) (500 mg, 2.63 mmol) in DMF (10 mL) was added imidazole (250 mg, 3.67 mmol) followed by TBSCl (515 mg, 3.42 mmol) at room temperature and the mixture was stirred for 7 h. Cold water (8 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (1 × 10 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 98:2) to provide 641 mg (80%) of **109** as a colorless liquid.

R_f = 0.33 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2956, 2930, 2858, 1693, 1598, 1493, 1256, 1110, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H, CO), 7.67 (d, 1H, J = 2.1 Hz,

Ar*H*), 7.62 (dd, 1H, *J* = 8.2, 2.1 Hz, Ar*H*), 6.88 (d, 1H, *J* = 8.2 Hz, Ar*H*), 5.36-5.27 (m, 1H, C=C*H*), 3.34 (d, 1H, *J* = 7.5 Hz, CH_2CH=C), 1.77 (br d, 3H, *J* = 0.9 Hz, CH_3), 1.70 (s, 3H, CH_3), 1.03 (s, 9H,C(CH_3)$_3$), 0.29 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2 (*C*HO), 159.3 (ArC_{ipso}), 133.6 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 133.3 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 131.4 (Ar*C*), 130.2 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 129.6 (Ar*C*), 121.5 (Ar*C* or H*C*=C(CH$_3$)$_2$), 118.4 (Ar*C* and H*C*=C(CH$_3$)$_2$, or 2 × Ar*C*), 28.4 (*C*H$_2$), 25.8 (*C*H$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 17.9 (*C*H$_3$), -4.1 (Si(*C*H$_3$)$_2$).

4-(Benzyloxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (101):



108 **101**

To a solution of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (**108**) (85 mg, 0.45 mmol) in DMF (1 mL) was added K_2CO_3 (74 mg, 0.54 mmol) followed by BnBr (64 µL, 0.54 mmol) at room temperature and the mixture was stirred for 5 h. Cold water (2 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 4 mL). The combined organic layers were washed with water (1 × 4 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to provide 101 mg (81%) of **101** as colorless liquid.

R_f = 0.32 (hexanes/EtOAc, 9:1); IR (neat): 2968, 2913, 2730, 1684, 1597, 1496, 1453, 1435, 1250, 1112, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H, C*H*O), 7.70 (s, 1H, Ar*H*), 7.69 (dd (partial overlap with s at 7.70), 1H, *J* = 8.2, 2.2 Hz, Ar*H*), 7.45-7.38

(m, 4H, Ar*H*), 7.37-7.32 (m, 1H, Ar*H*) 6.99 (d, 1H, *J* = 8.2 Hz, Ar*H*), 5.34-5.29 (m 1H, C=C*H*), 5.18 (s, 2H, PhCH_2), 3.41 (d, 1H, *J* = 7.3 Hz, CH_2CH=), 1.75 (br s, 3H, CH_3), 1.65 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3 (*C*HO), 161.6 (ArC_{ipso}), 136.4 (ArC_{ipso}), 133.6 (ArC_{ipso}), 131.5 (ArC_{ipso} or C=*C*$(CH_3)_2$), 130.65 (Ar*C*), 130.63 (Ar*C*), 129.9 (ArC_{ipso} or C=*C*$(CH_3)_2$), 128.8 (2 × Ar*C*), 128.2 (Ar*C*), 127.3 (2 × Ar*C*), 121.5 (H*C*=C$(CH_3)_2$), 111.3 (Ar*C*), 70.3 (Ph*C*H_2), 28.7 (H_2*C*H*C*=C), 25.9 (*C*H_3), 17.9 (*C*H_3); HRMS (ESI, pos.): *m/z* 280.1467 (280.1463 calc. for $C_{19}H_{20}O_2$, $(M)^+$), 281.1535 (281.1542 calc. for $C_{19}H_{21}O_2$, $(M+H)^+$) and 303.1356 (303.1361 calc. for $C_{19}H_{20}NaO_2$, $(M+Na)^+$).

4.7 References

1. Sadamitsu, Y.; Komatsuki, K.; Saito, K.; Yamada, T. *Org. Lett.* **2017**, *19*, 3191.

2. Bernier, D.; Brückner, R. *Synthesis* **2007**, 2249.

3. Cruz, P. G.; Auld, D. S.; Schultz, P. J.; Lovell, S.; Battaile, K. P.; MacArthur, R.; Shen, M.; Tamayo-Castillo, G.; Inglese, J.; Sherman, D. H. *Chem. Biol.* **2011**, *18*, 1442.

4. Xu, H.-W.; Xu, C.; Fan, Z.-Q.; Zhao, L.-J.; Liu, H.-M. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 737.

5. Campbell, A. C.; Maidment, M. S.; Pick, J. H.; Stevenson, D. F. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1567.

6. Knight, D.W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 70.

7. Ramage, R.; Griffiths, G.J.; Shutt, F. E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1539.

8. Gill, M.; Kiefel, M. J.; Lally, D. A.; Ten, A. *Aust. J. Chem.* **1990**, *43*, 1497.

9. Antane, S.; Caufield, C. E.; Hu, W.; Keeney, D.; Labthavikul, P.; Morris, K.; Naughton, S. M.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 176.

10. Kaczybura, N.; Brückner, R. *Synthesis* **2007**, 118.

11. Nadal, B.; Rouleau, J.; Besnard, H.; Thuéry, P.; Gall, T. L. *Tetrahedron* **2011**, *67*, 2605.

12. Sadamitsu, Y.; Komatsuki, K.; Saito, K.; Yamada. T. *Org. Lett.*, **2017**, *19*, 3191.

13. Manchoju, A.; Pansare, S. V. *Org. Lett.* **2016**, *18*, 5952.

14. Eicher, T.; Tiefensee, K.; Dönig, R.; Pick, R. *Synthesis*, **1991**, 98.

15. Sugiyaman, H.; Ojima, B.; Kobayashyi, M.; Senda, S.; Ishiyama, J.-I.; Seto, S. *Agric. Biol. Chem.*, **1979**, *43*, 403.

16. Ojima, N.; Takenaka, S.; Seto, S. *Phytochemistry* **1975**, *14*, 573.

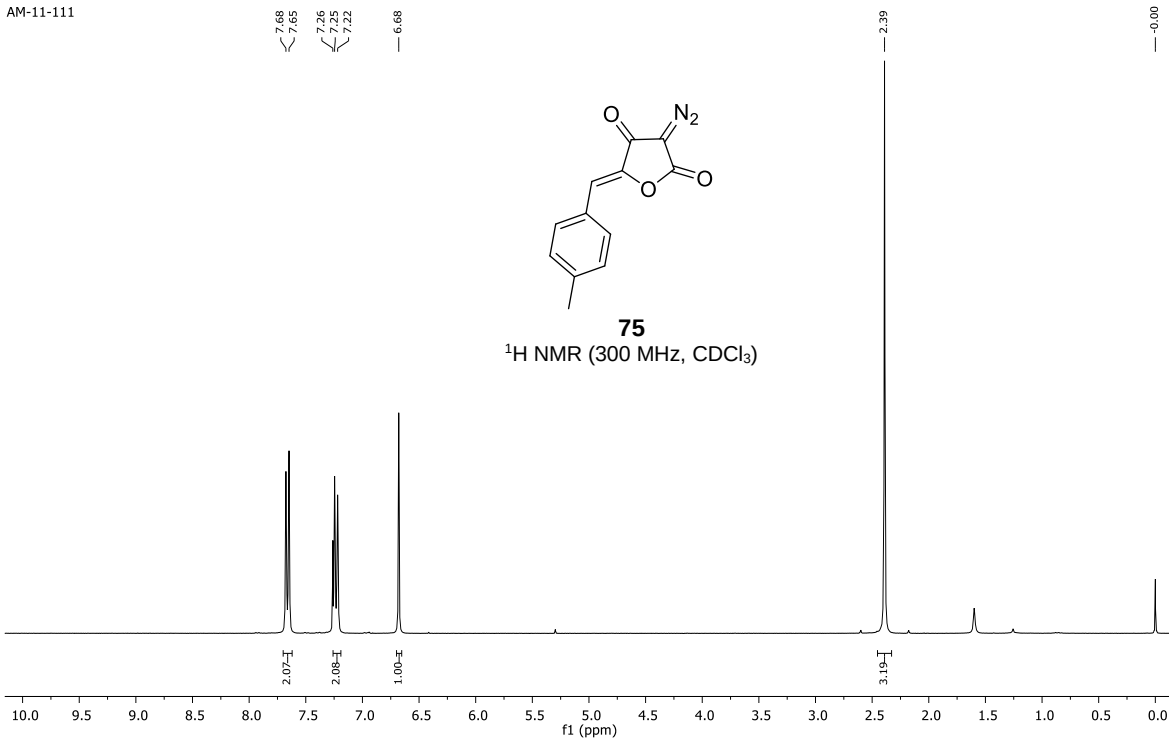
17. Tripathi, R. P.; Bisht, S. S.; Pandey, V. P.; Pandey, S. K.; Singh, S.; Sinha, S. K.; Chaturvedi, V. *Med. Chem. Res.* **2010**, *20*, 1515.

18. Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, *76*, 9353.

19. Naik, M. M.; Kamat, D. P.; Tilve, S. G.; Kamat, V. P. *Tetrahedron* **2014**, *70*, 5221.

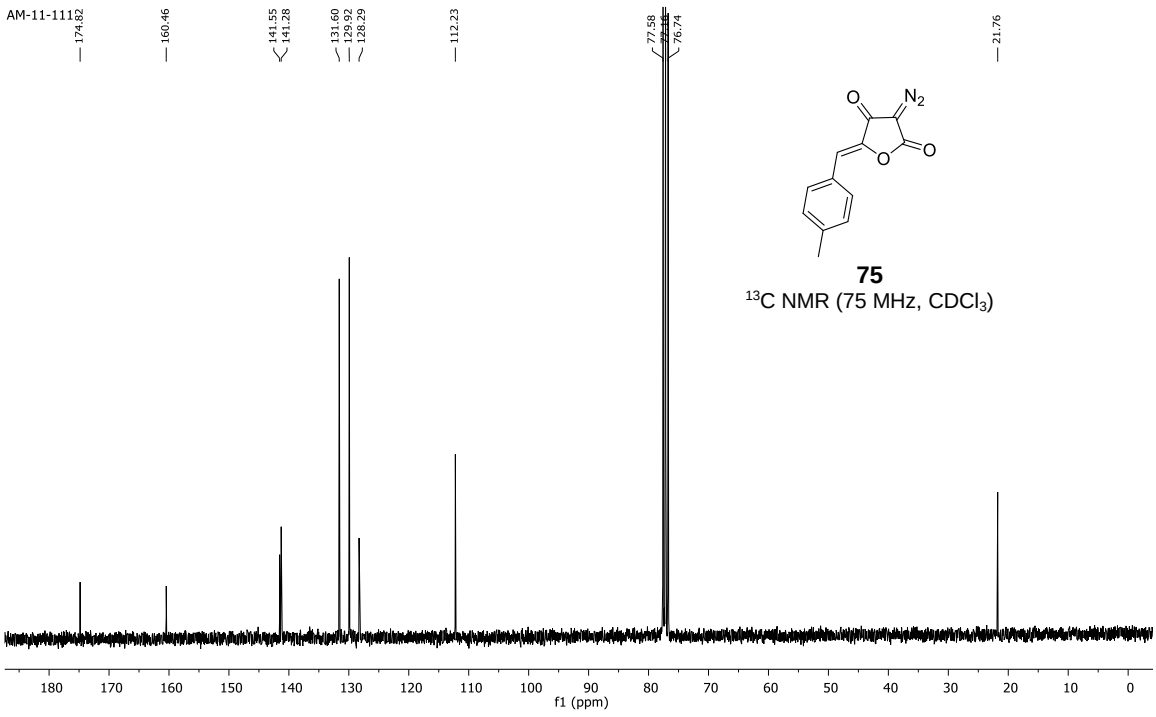
20. (a) Moriarty, R. M.; Grubjesic, S.; Surve, B. C.; Chandersekera, S. N.; Prakash, O.; Naithani, R. *Eur. J. Med. Chem.* **2006**, *41*, 263. (b) Weng, J.-Q.; Ali, A.; Estep, A.; Becnel, J.; Meyer, S. L. F.; Wedge, D. E.; Jacob, M.; Rimando, A. M. *Chem. Biodiversity* **2016**, *13*, 1165.

4.8 Selected ^{1}H NMR and ^{13}C NMR Spectra



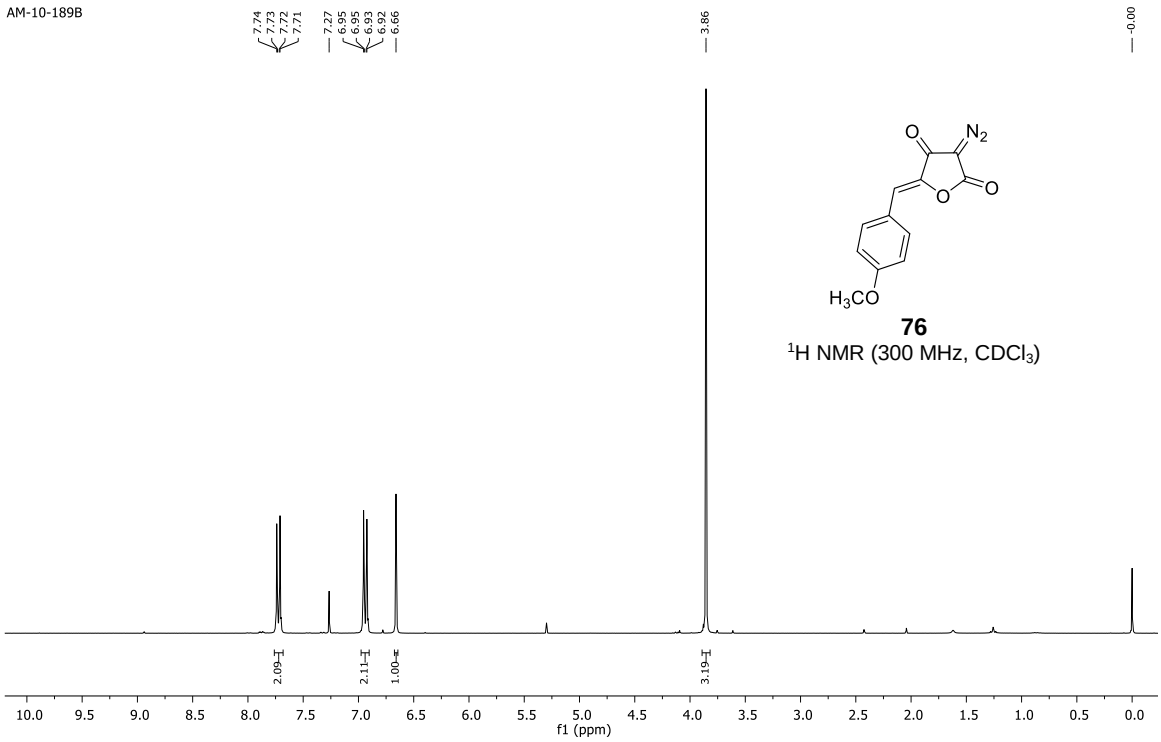
75

^{1}H NMR (300 MHz, $CDCl_3$)



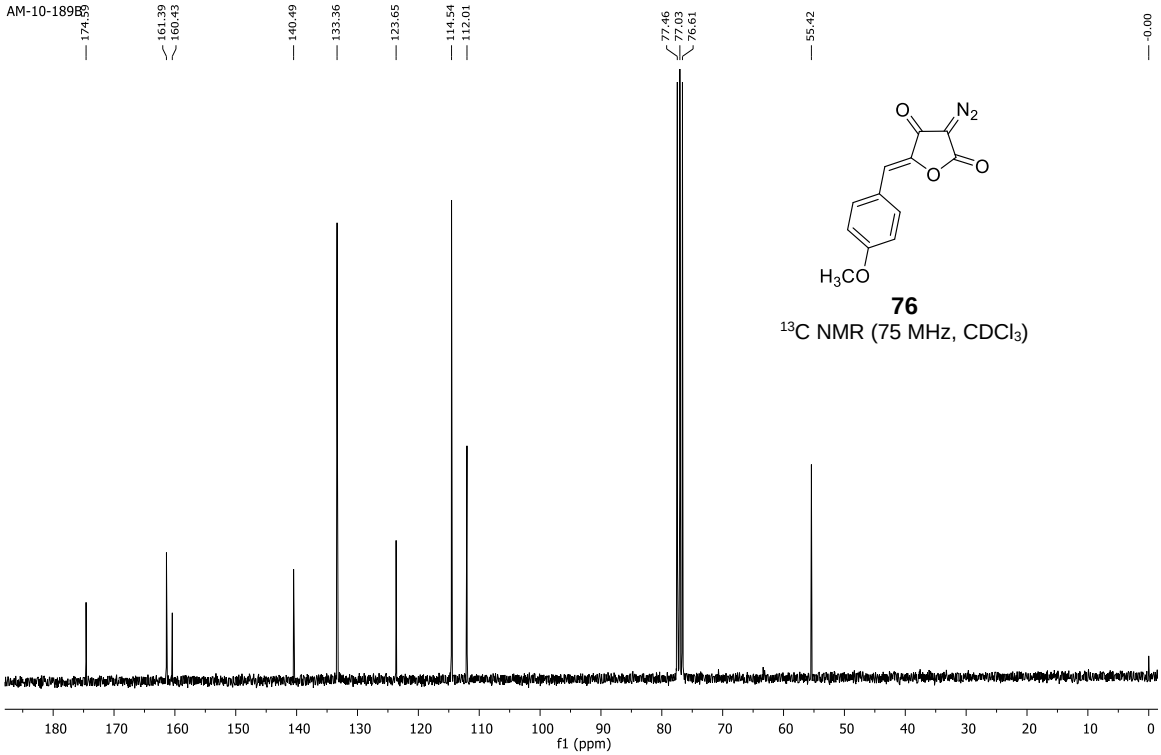
75

^{13}C NMR (75 MHz, $CDCl_3$)



76

^{1}H NMR (300 MHz, $CDCl_3$)



76

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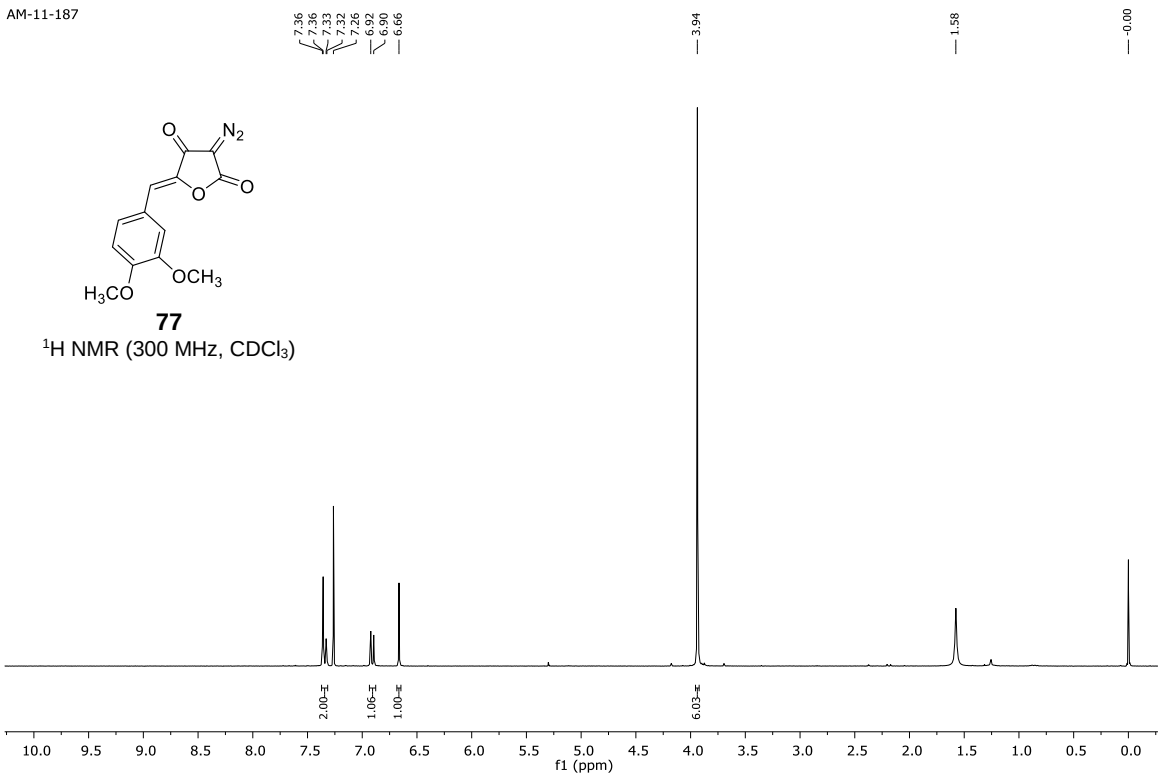

77

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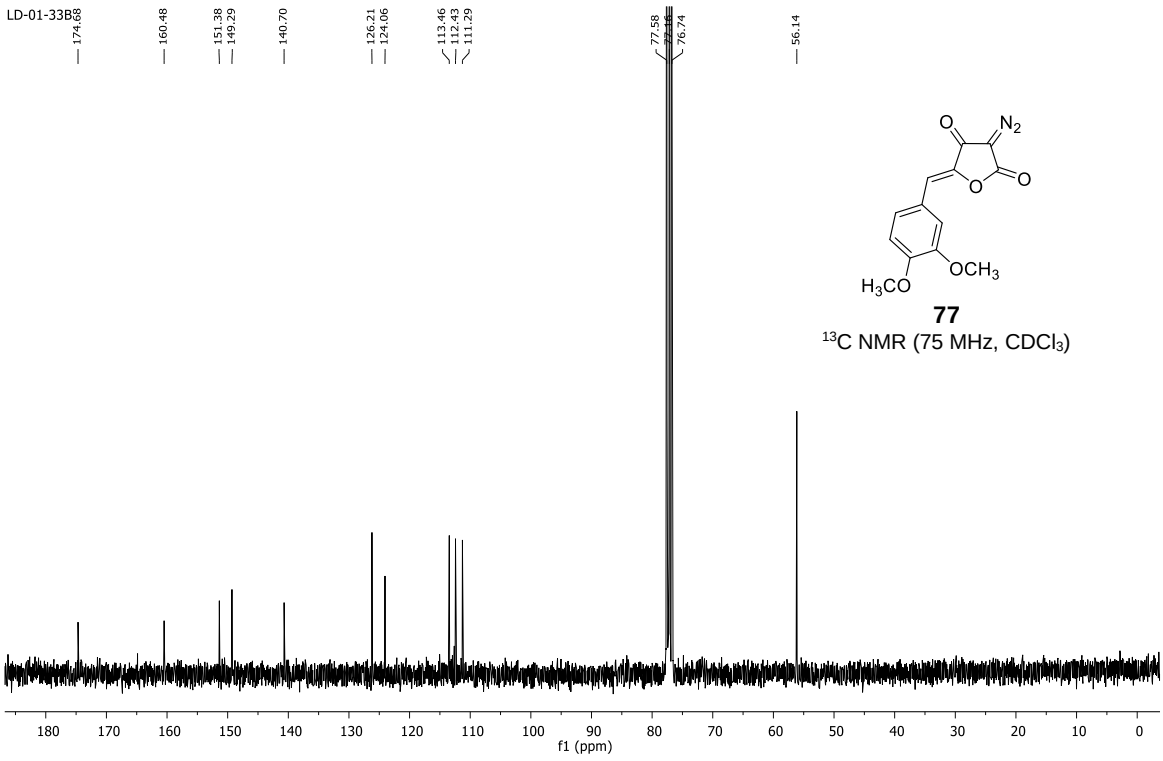

77

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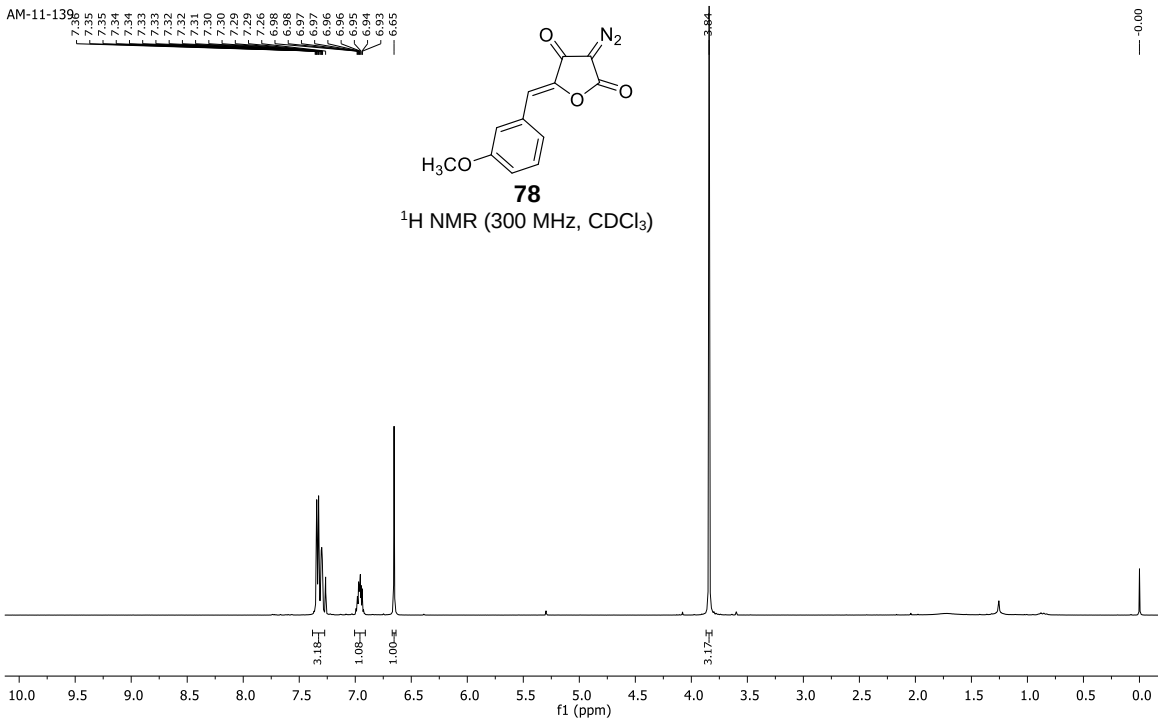
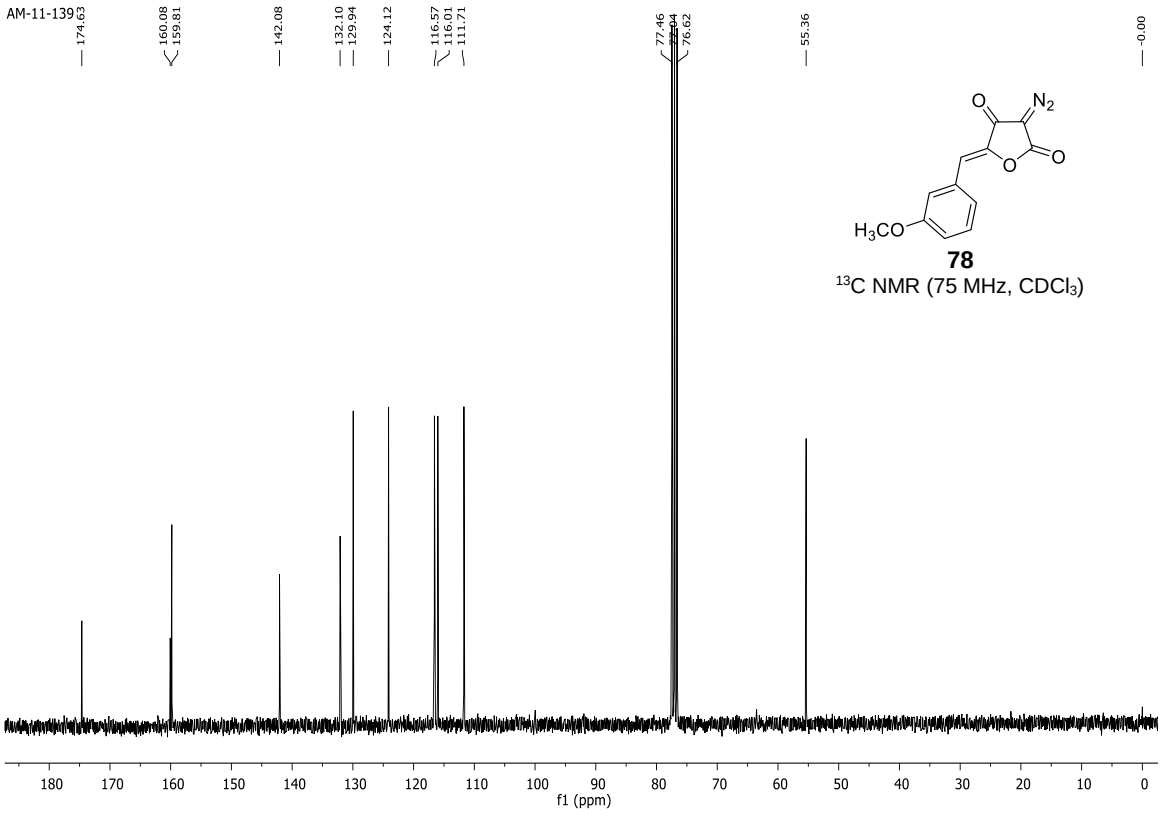


78

^{1}H NMR (300 MHz, $CDCl_3$)



78

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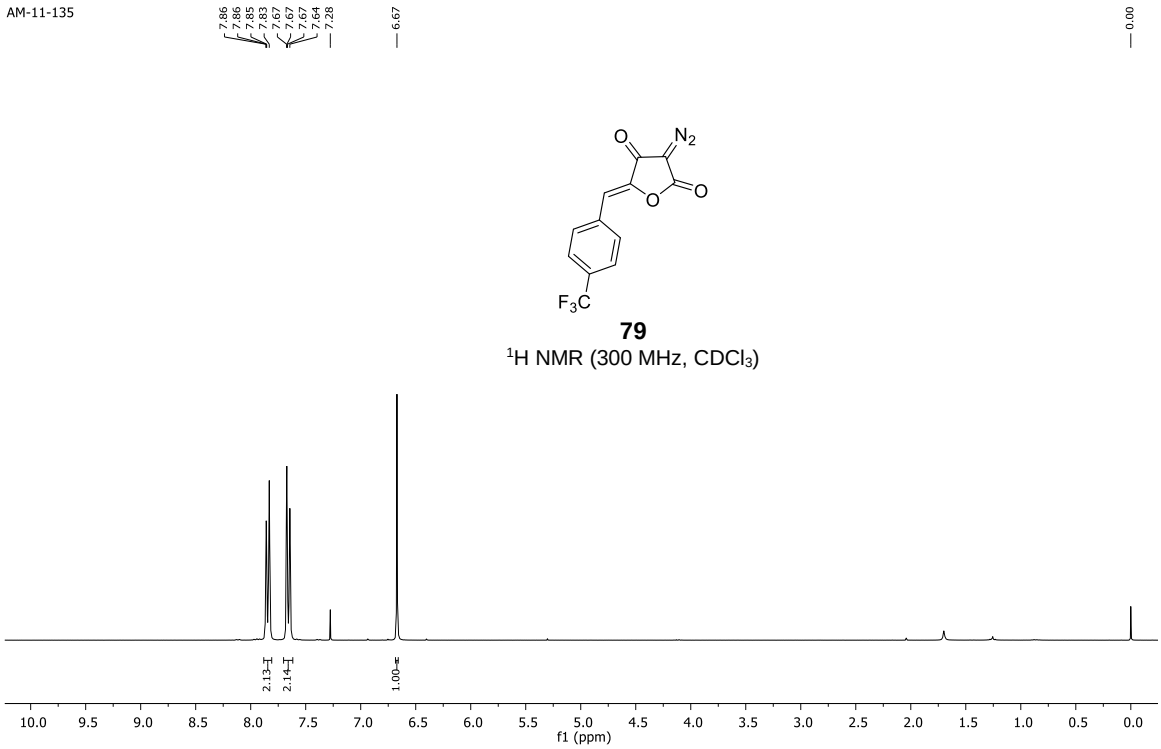
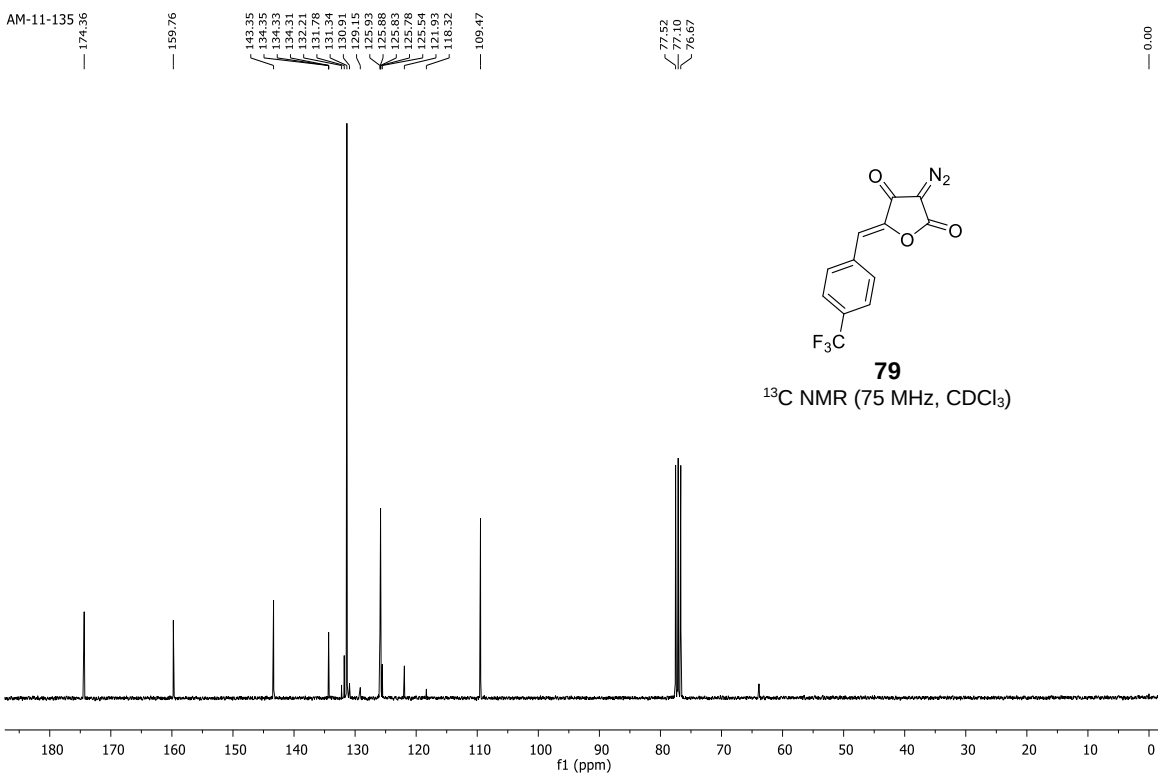


79

^{1}H NMR (300 MHz, $CDCl_3$)



79

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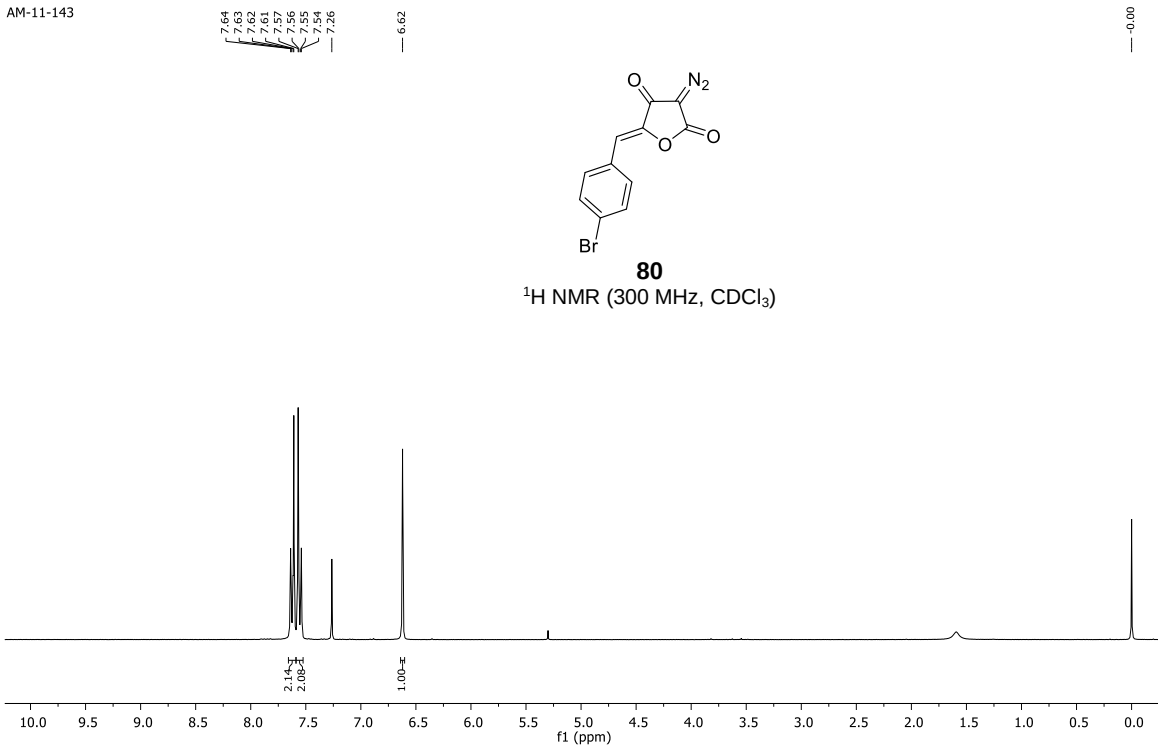
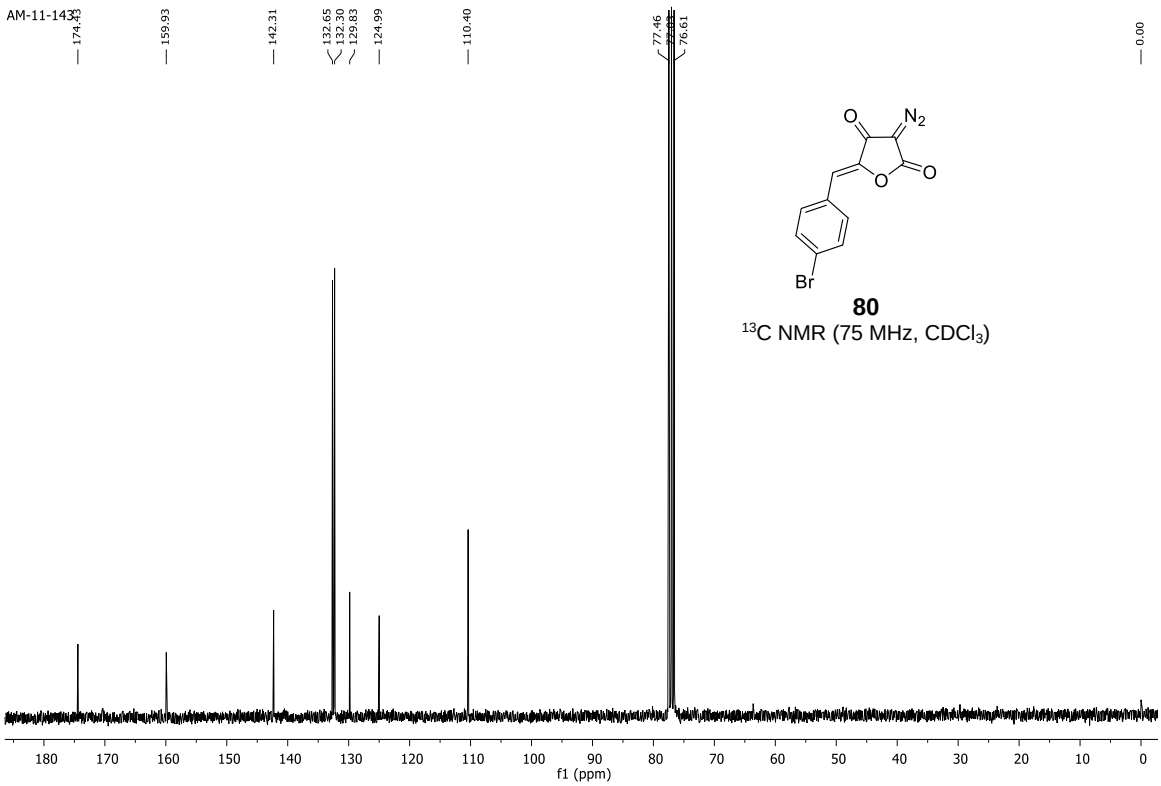


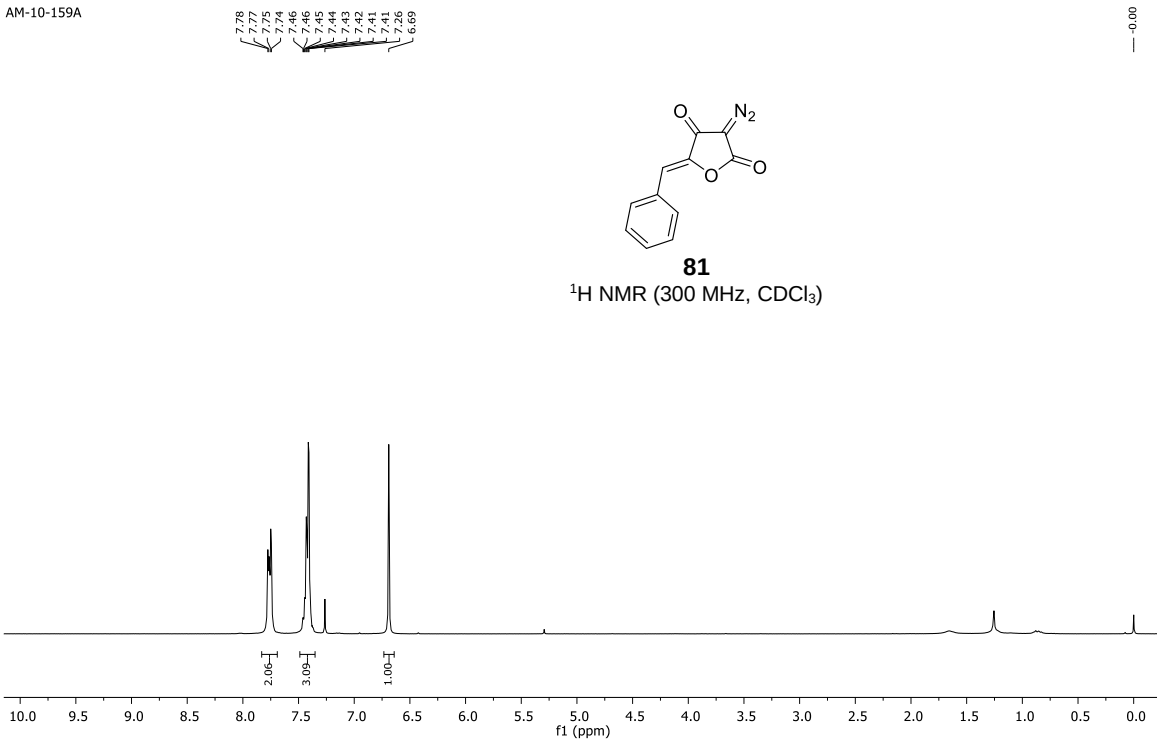
80

^{1}H NMR (300 MHz, $CDCl_3$)



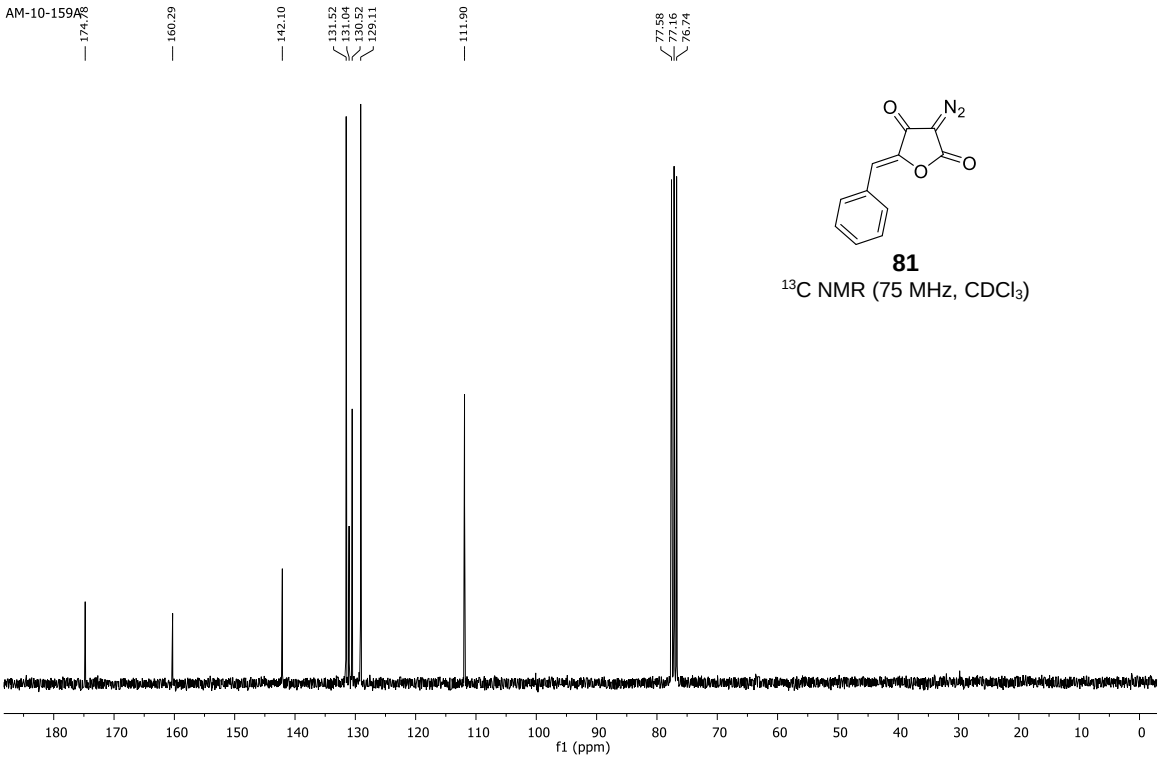
80

^{13}C NMR (75 MHz, $CDCl_3$)



81

^{1}H NMR (300 MHz, $CDCl_3$)



81

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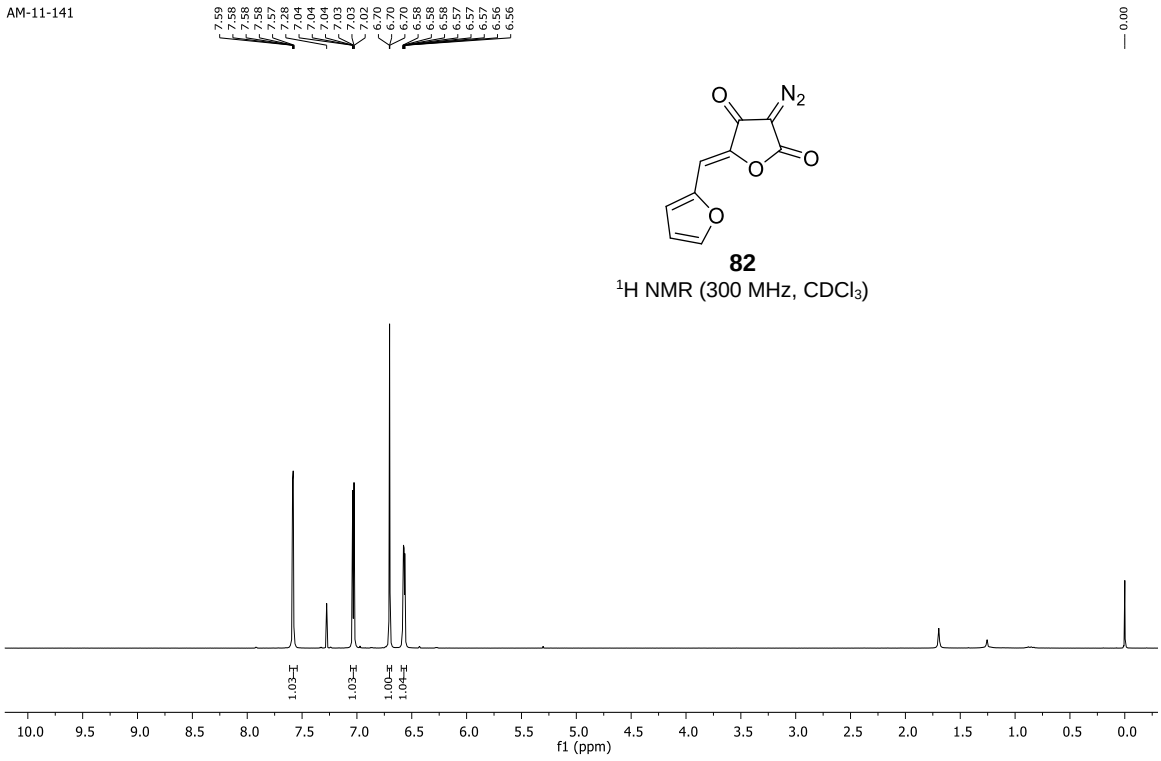
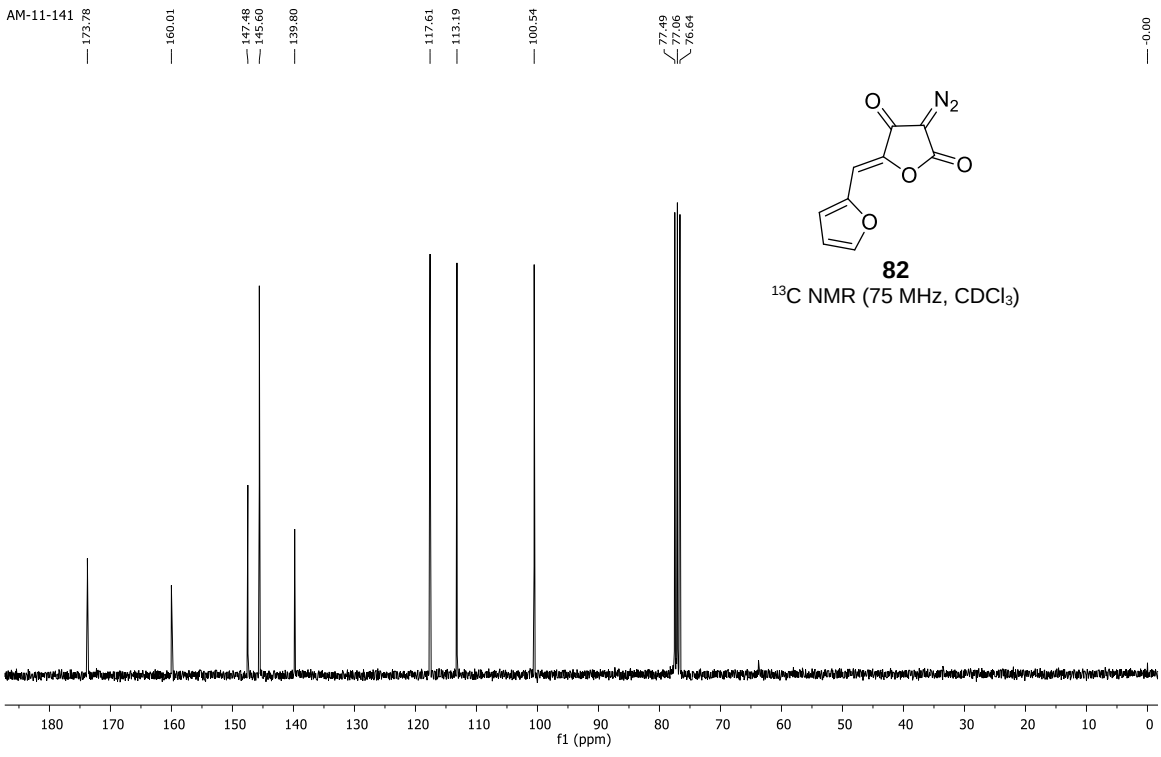


82

^{1}H NMR (300 MHz, $CDCl_3$)



82

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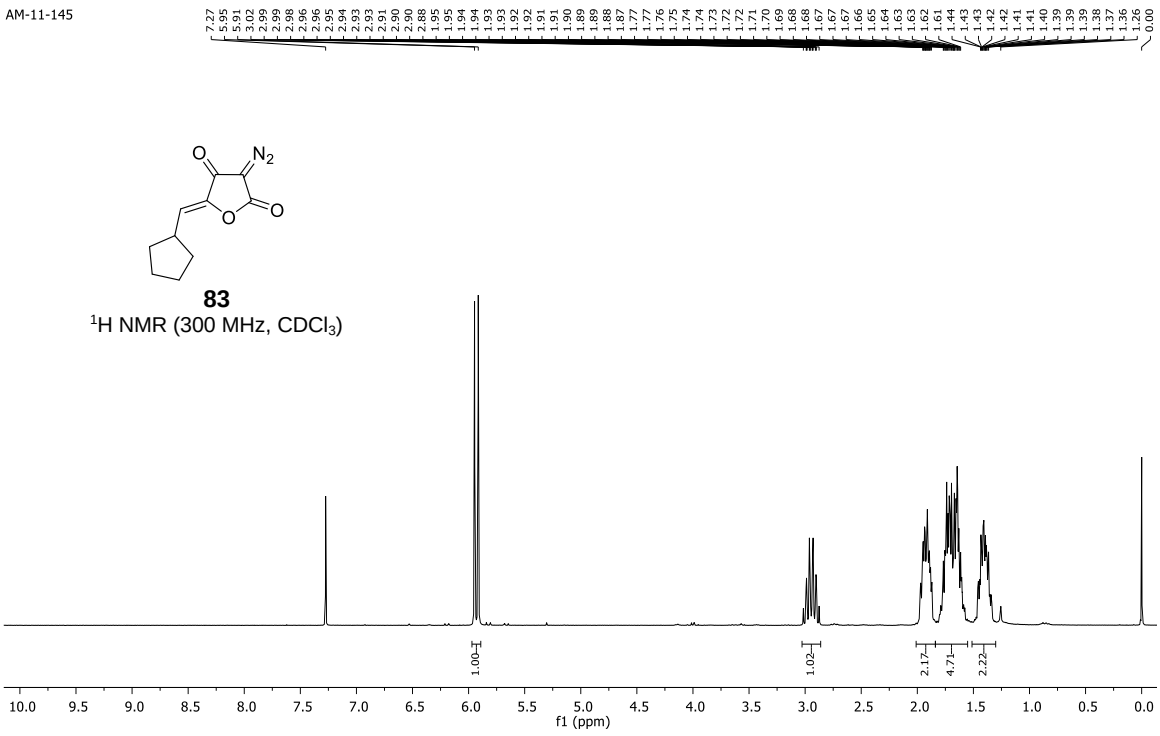

83

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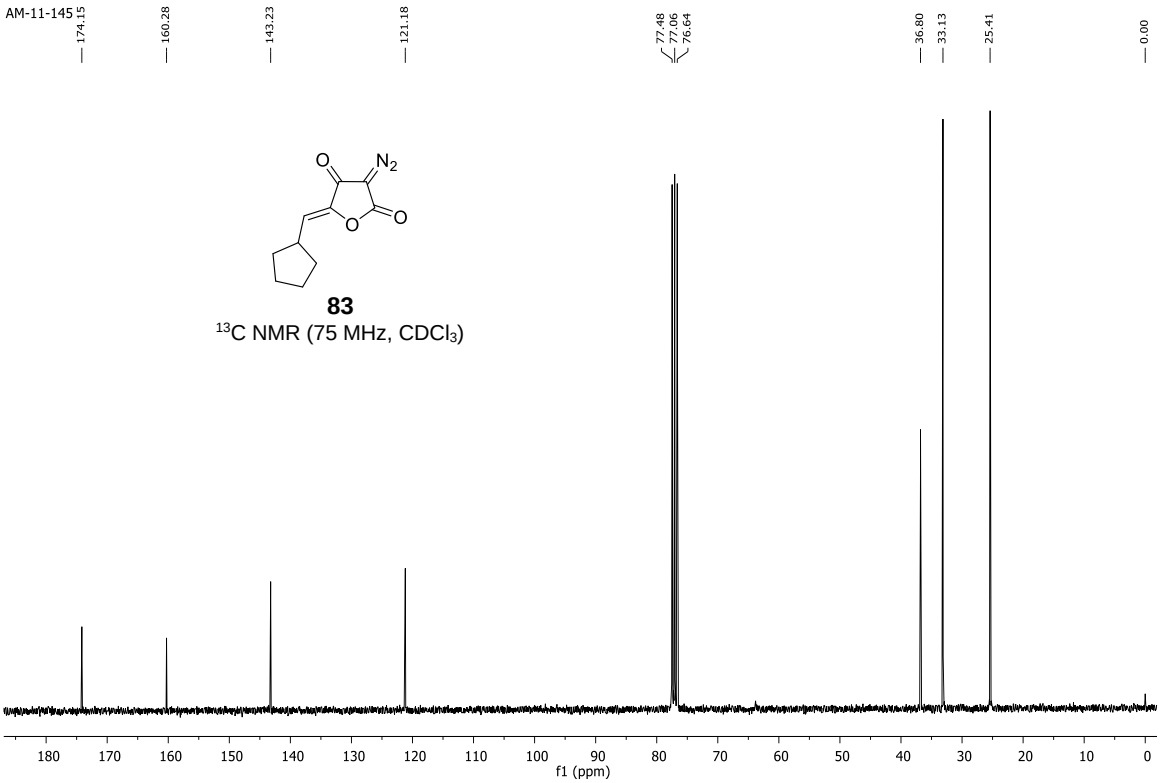
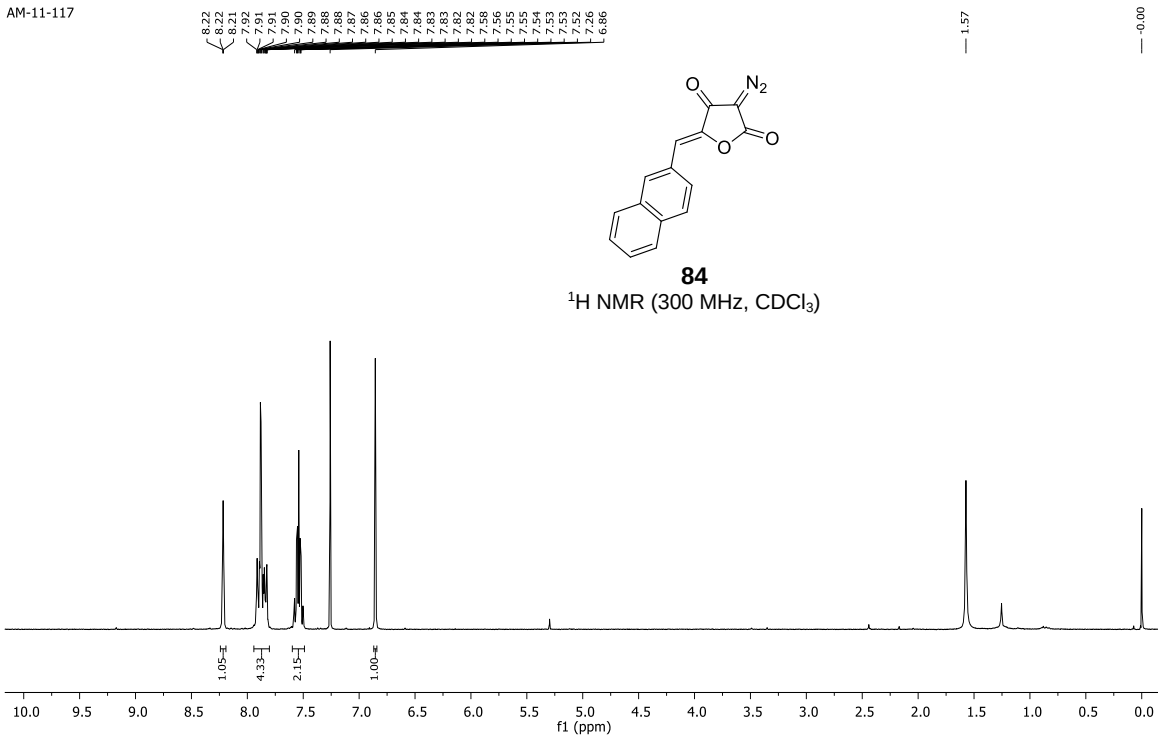


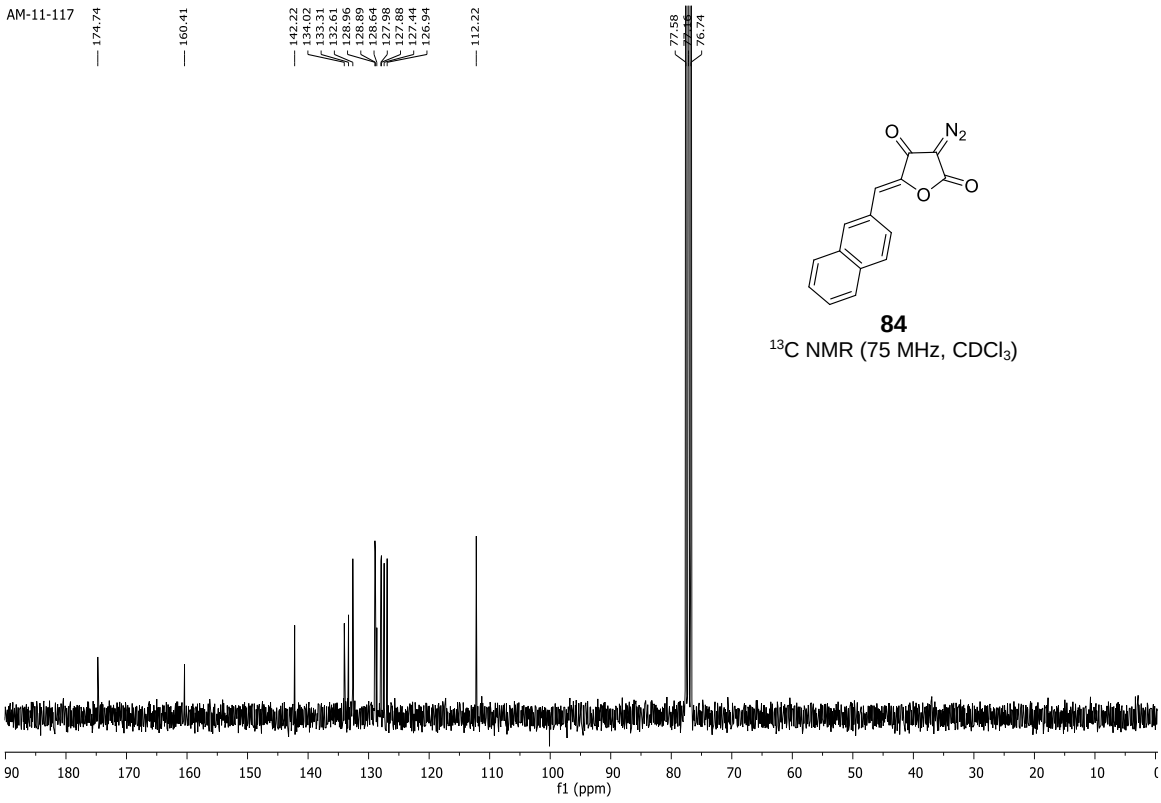
83

^{13}C NMR (75 MHz, $CDCl_3$)



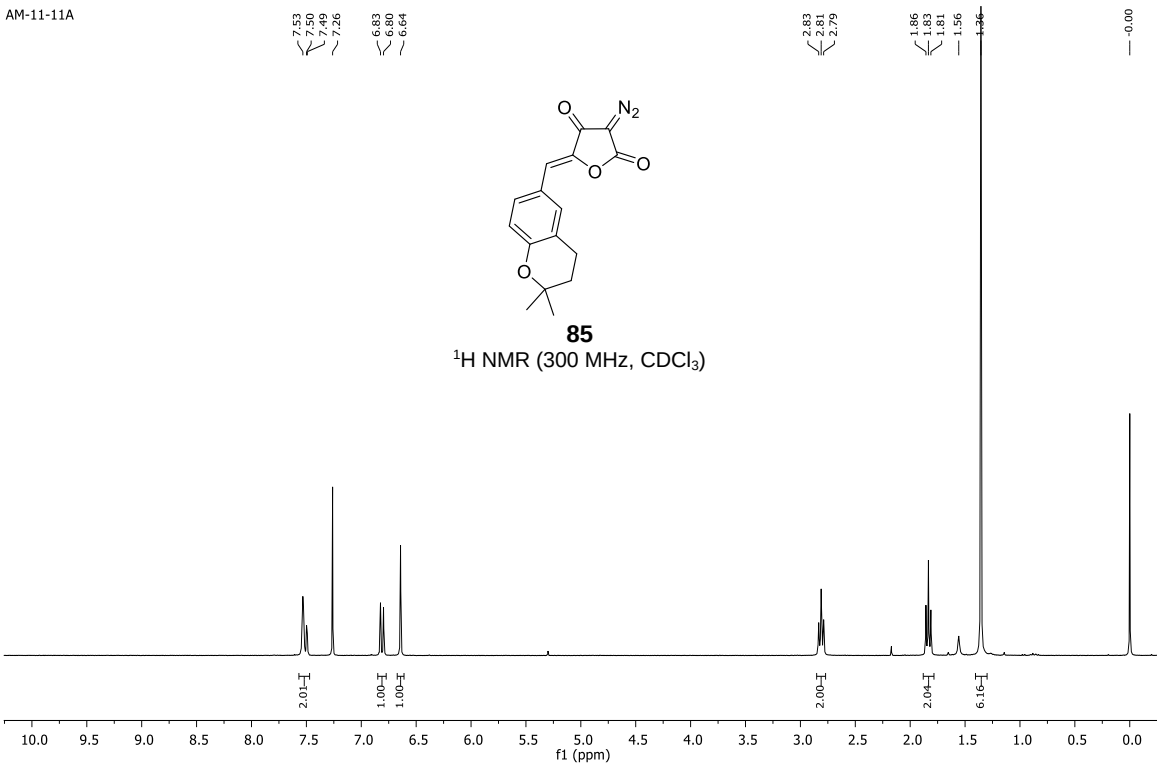
84

^{1}H NMR (300 MHz, $CDCl_3$)



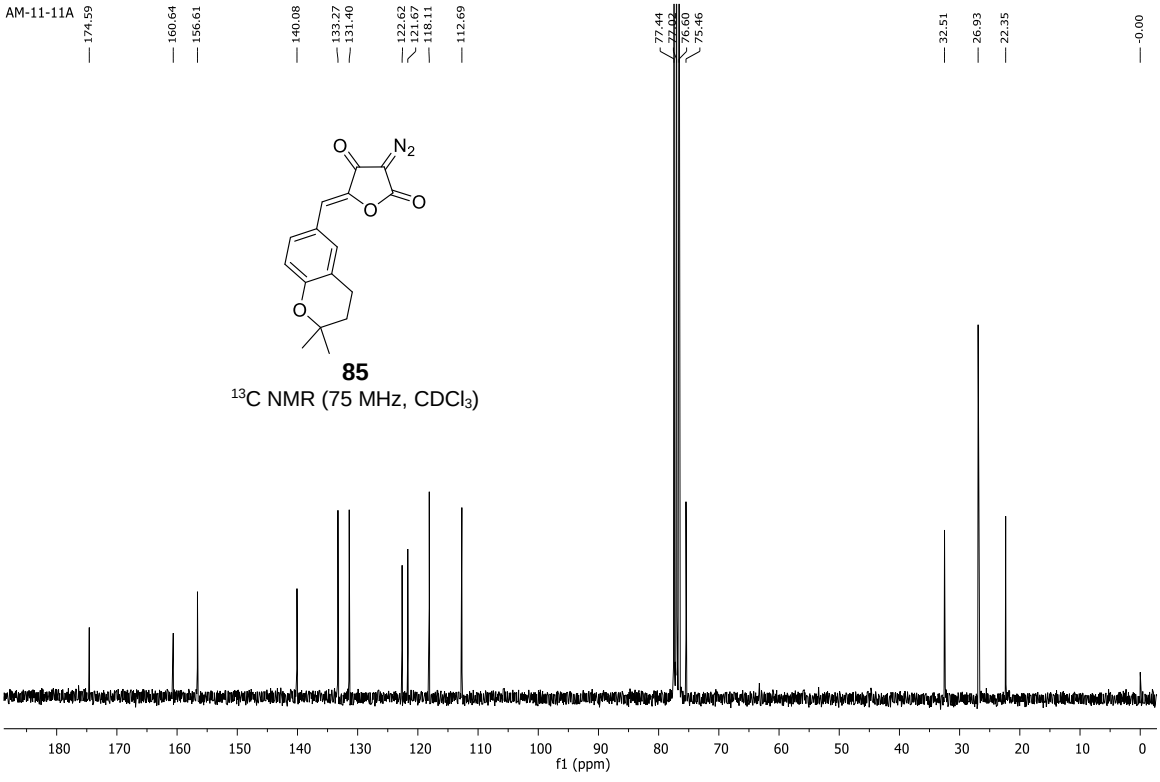
84

^{13}C NMR (75 MHz, $CDCl_3$)



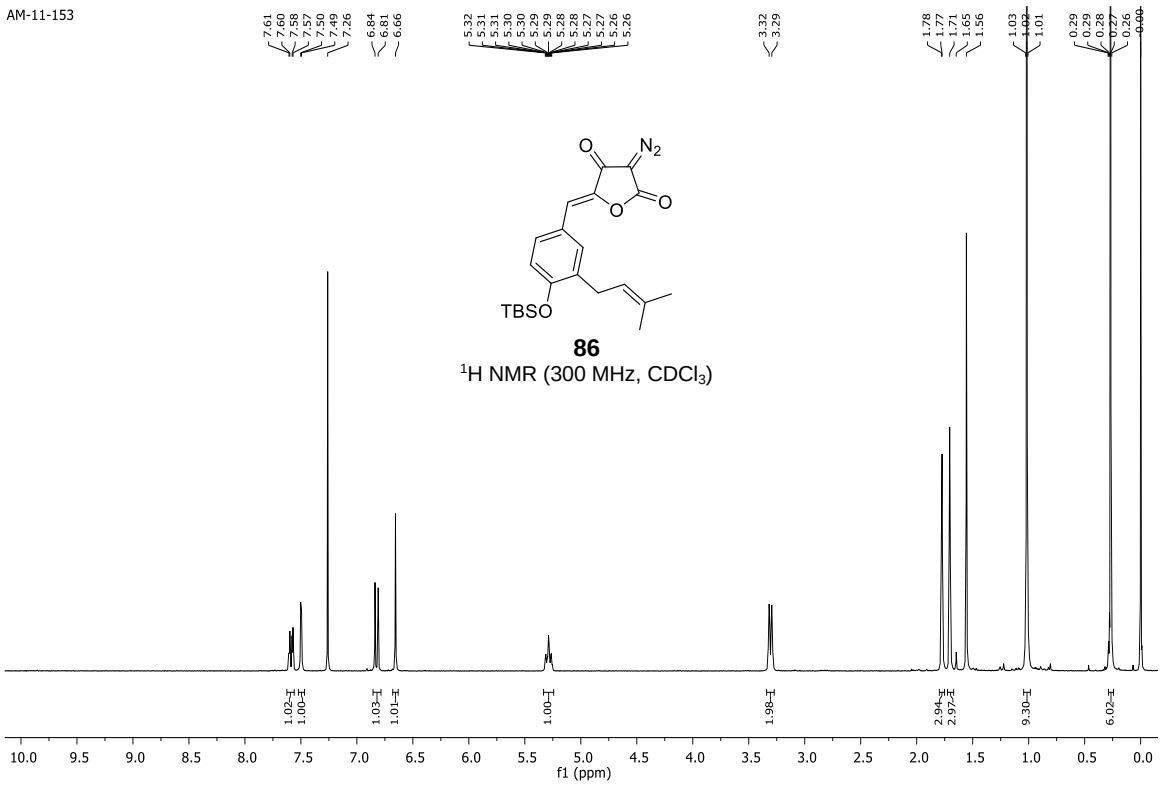
85

^{1}H NMR (300 MHz, $CDCl_3$)



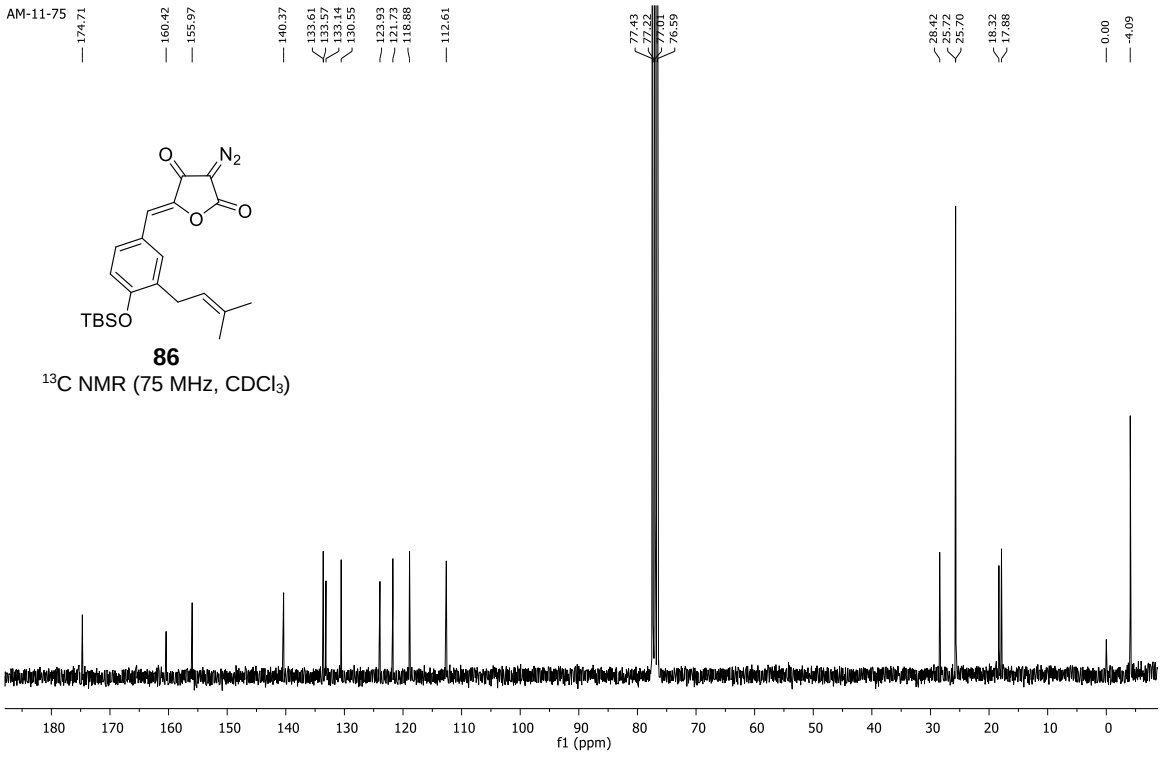
85

^{13}C NMR (75 MHz, $CDCl_3$)



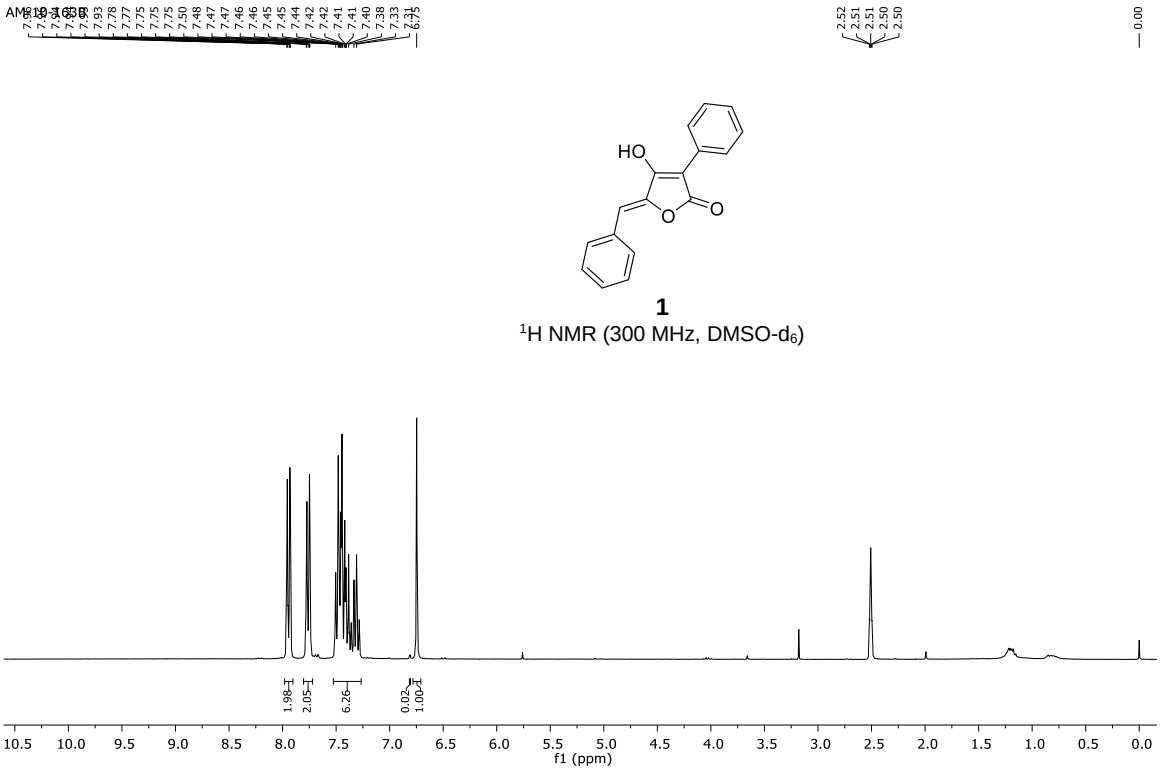
86

^{1}H NMR (300 MHz, $CDCl_3$)



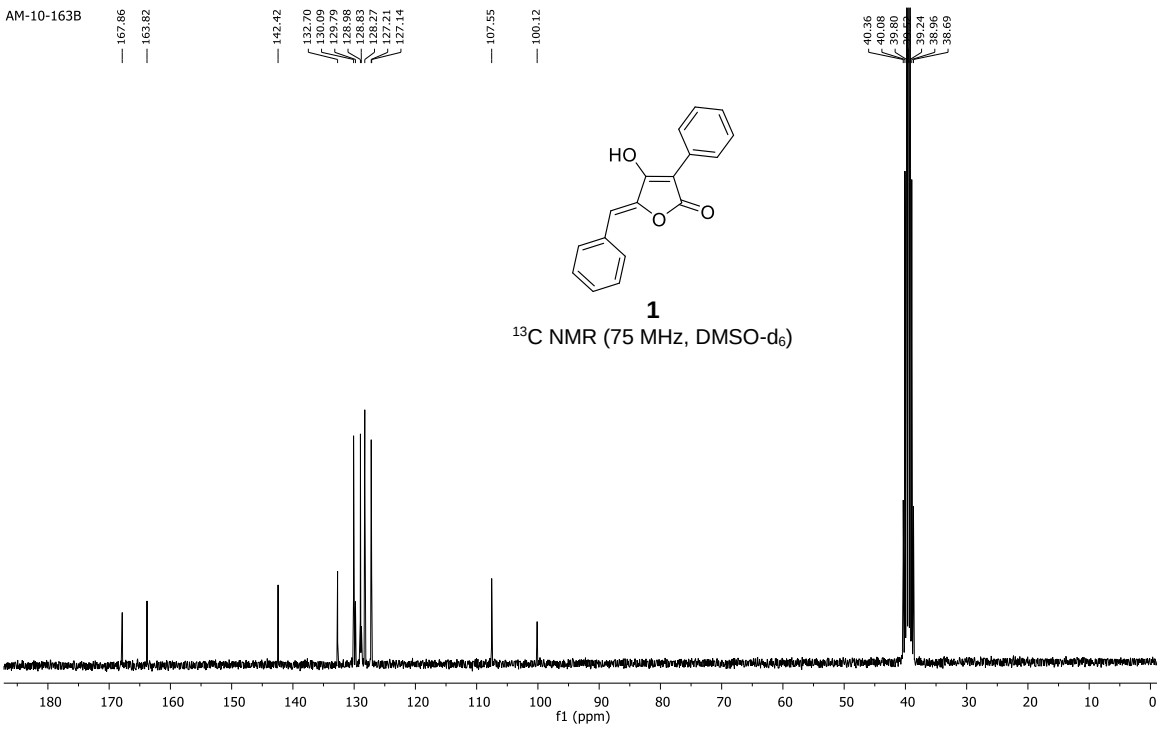
86

^{13}C NMR (75 MHz, $CDCl_3$)



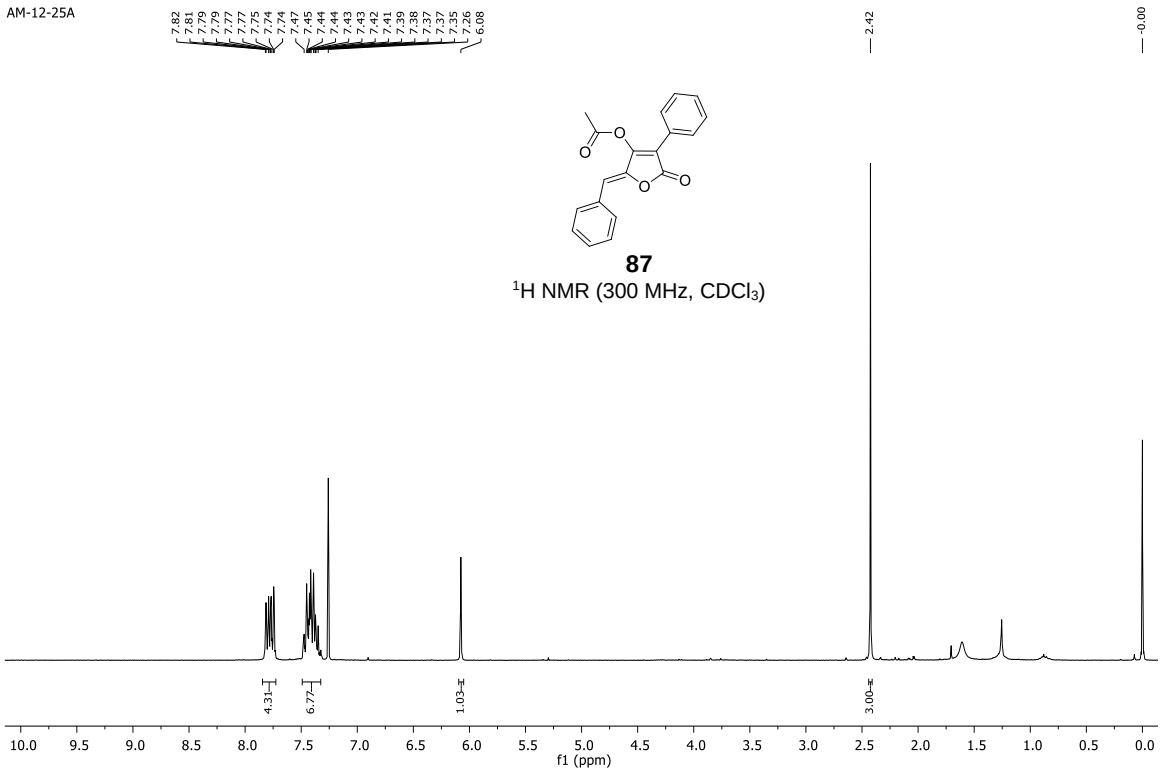
1

^{1}H NMR (300 MHz, DMSO-d_6)



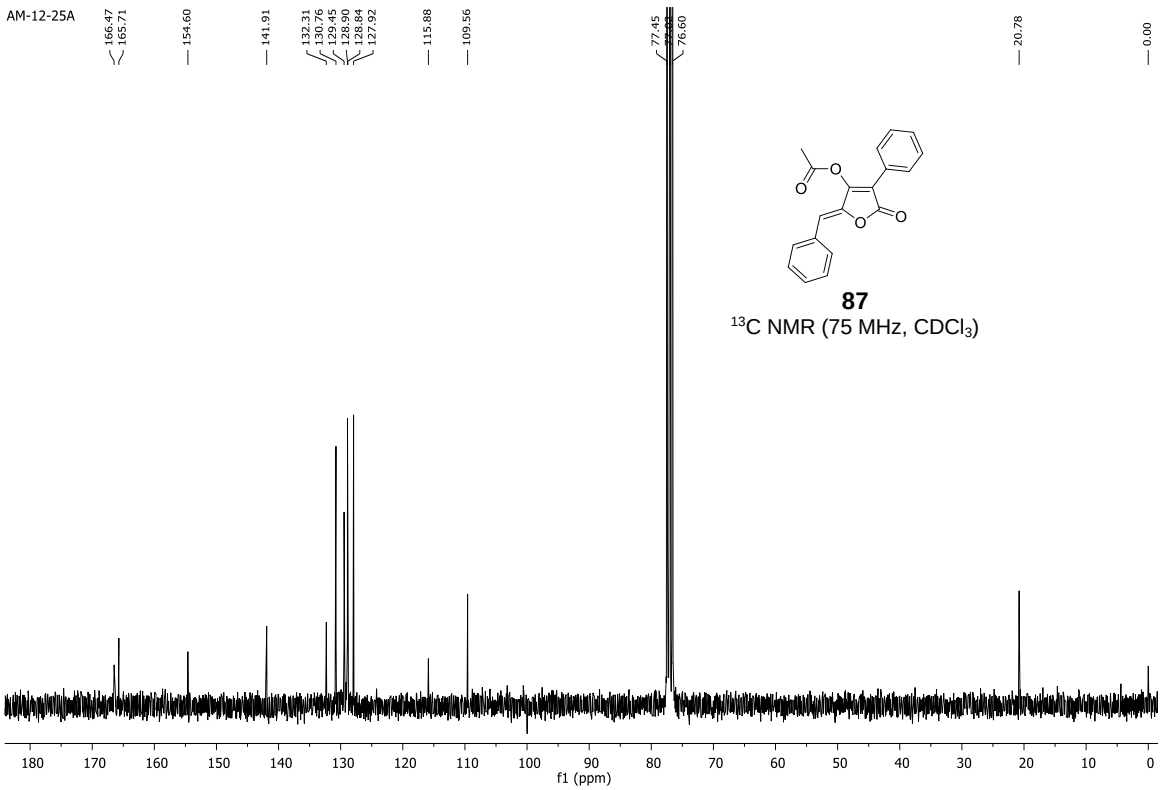
1

^{13}C NMR (75 MHz, DMSO-d_6)



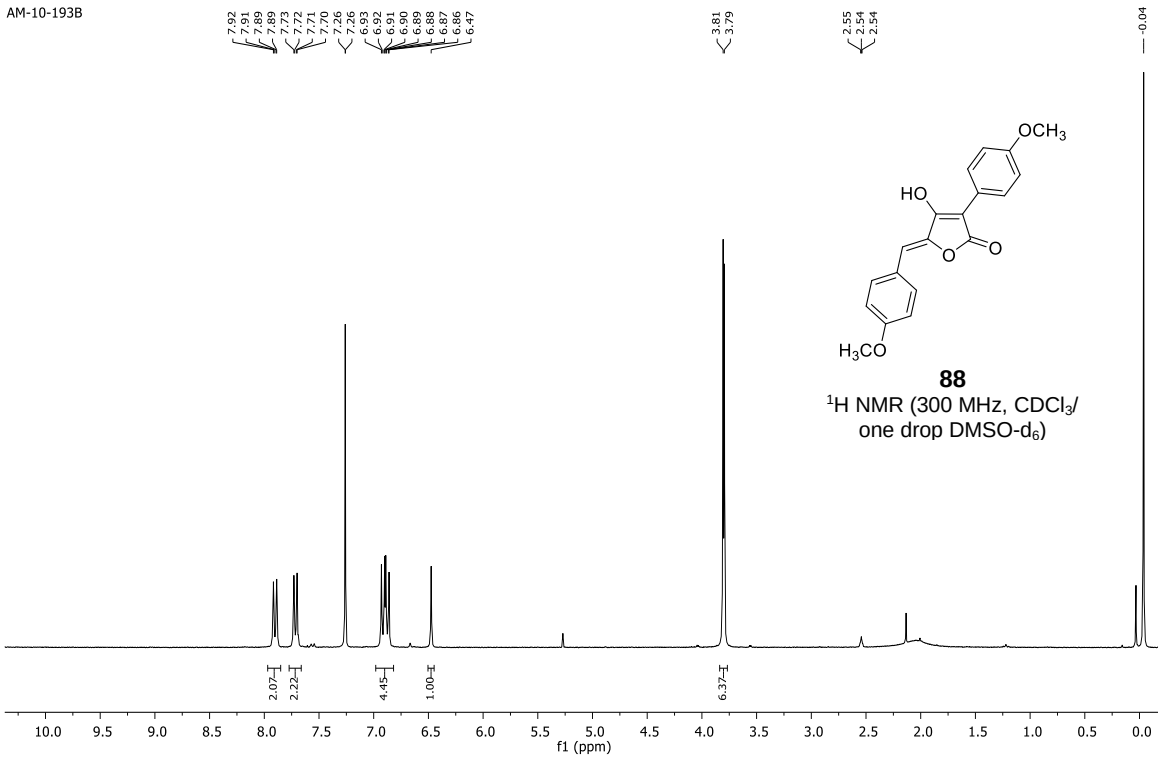
87

^{1}H NMR (300 MHz, $CDCl_3$)



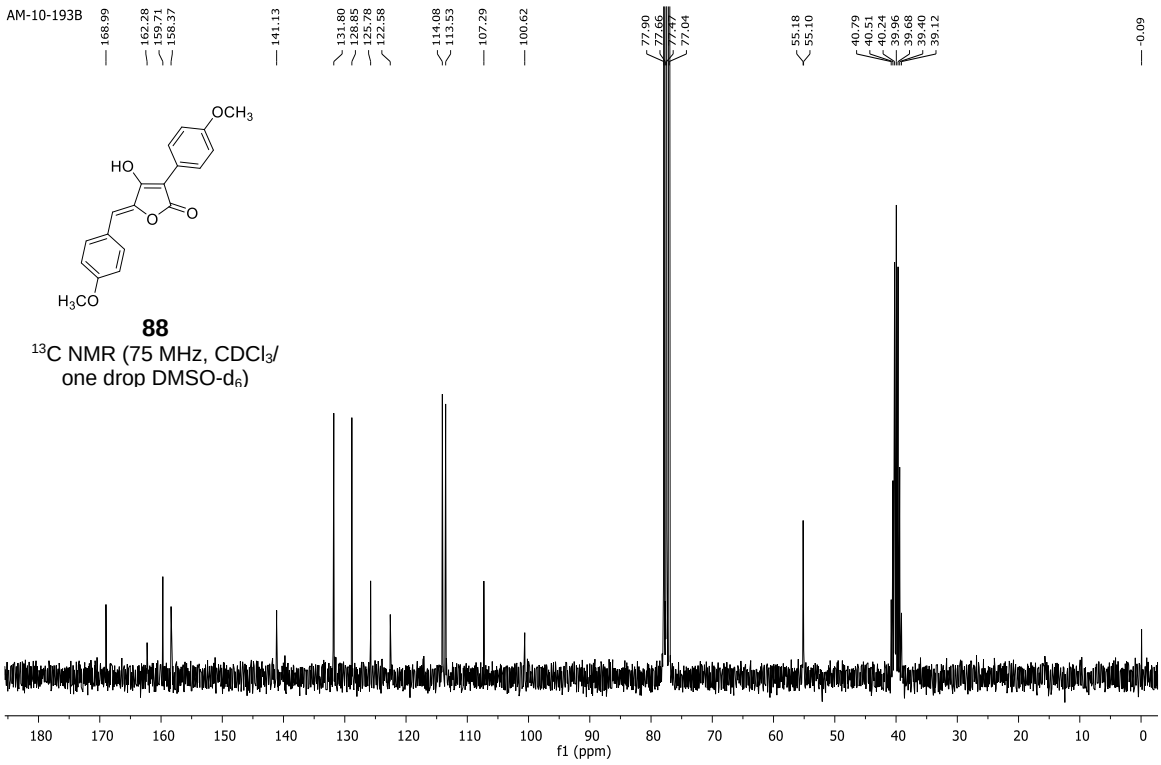
87

^{13}C NMR (75 MHz, $CDCl_3$)



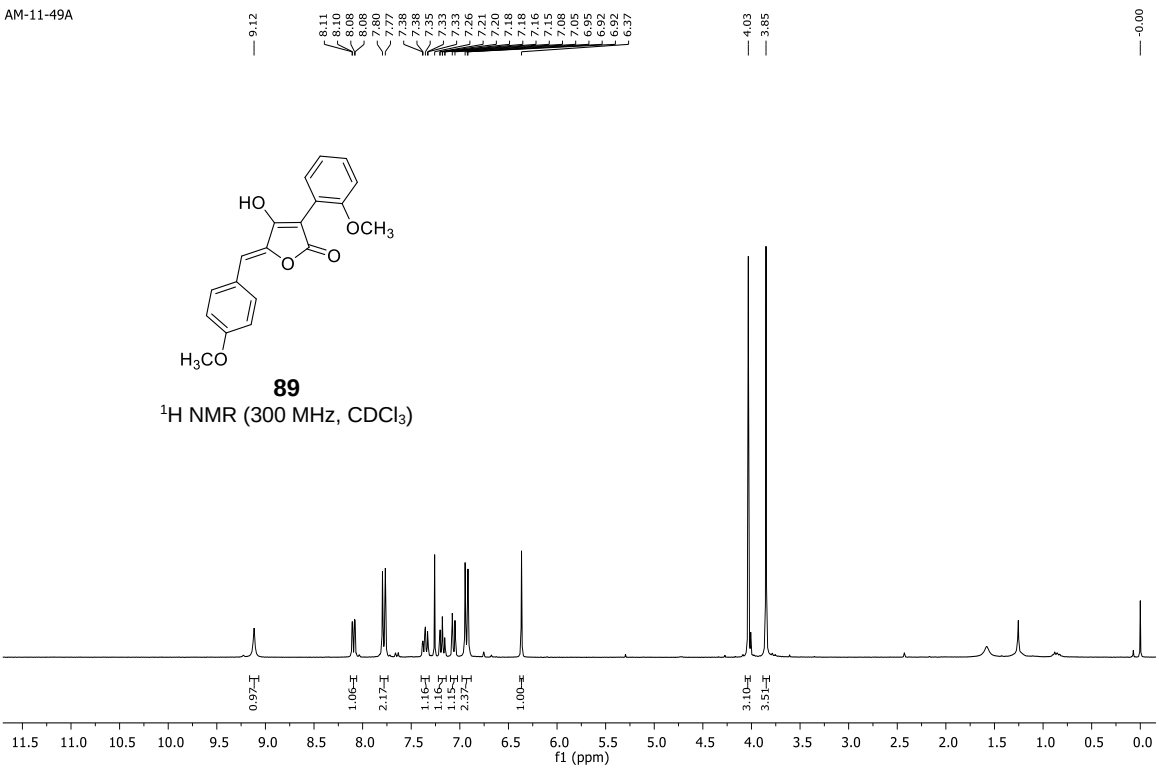
88

^{1}H NMR (300 MHz, $CDCl_3$/ one drop DMSO-d_6)



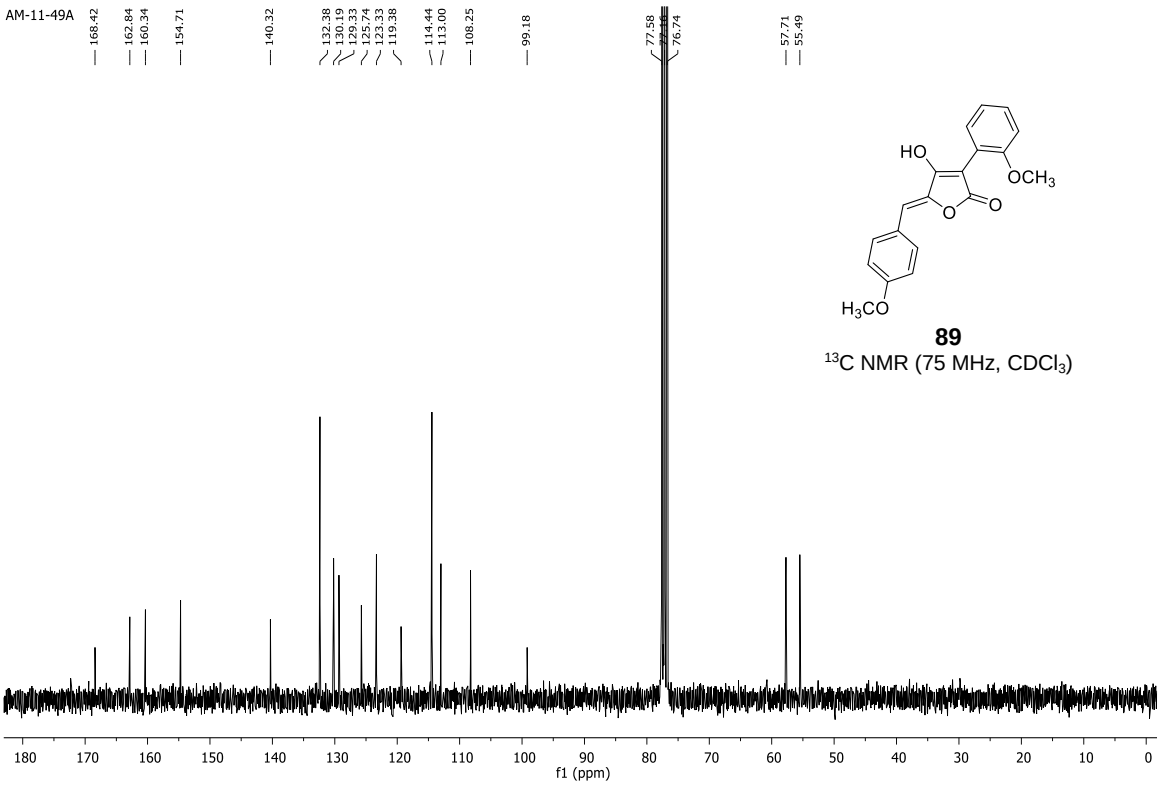
88

^{13}C NMR (75 MHz, $CDCl_3$/ one drop DMSO-d_6)



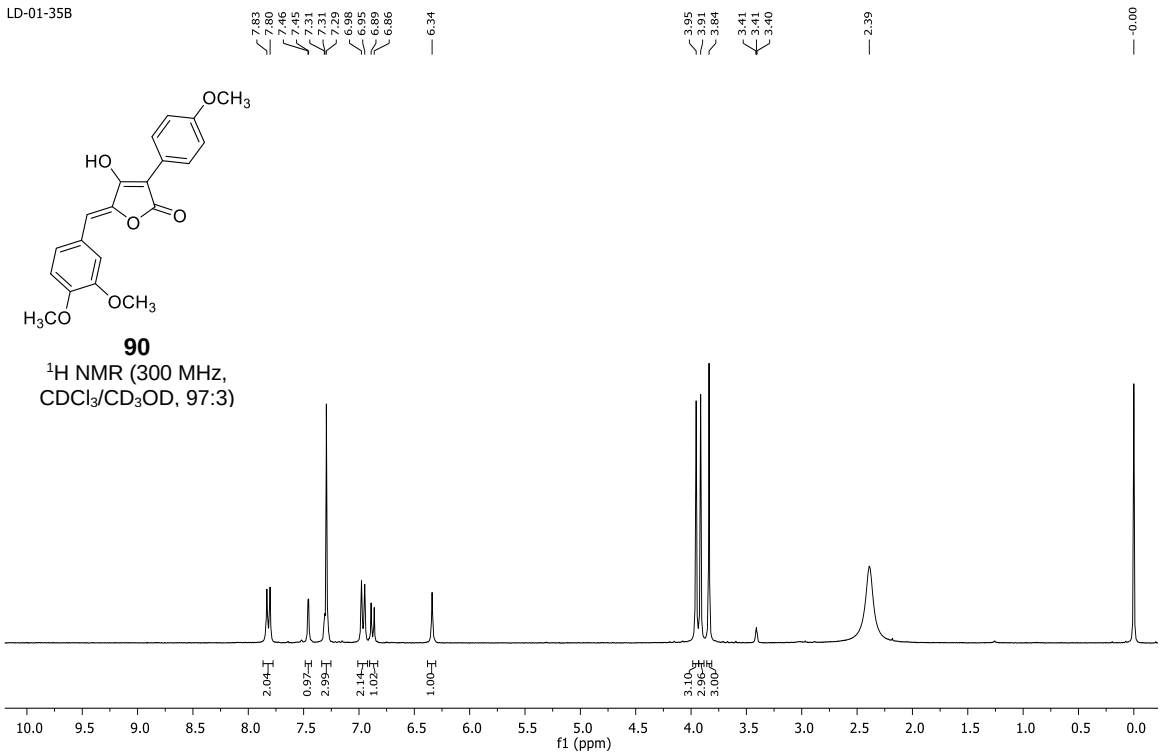
89

^{1}H NMR (300 MHz, $CDCl_3$)



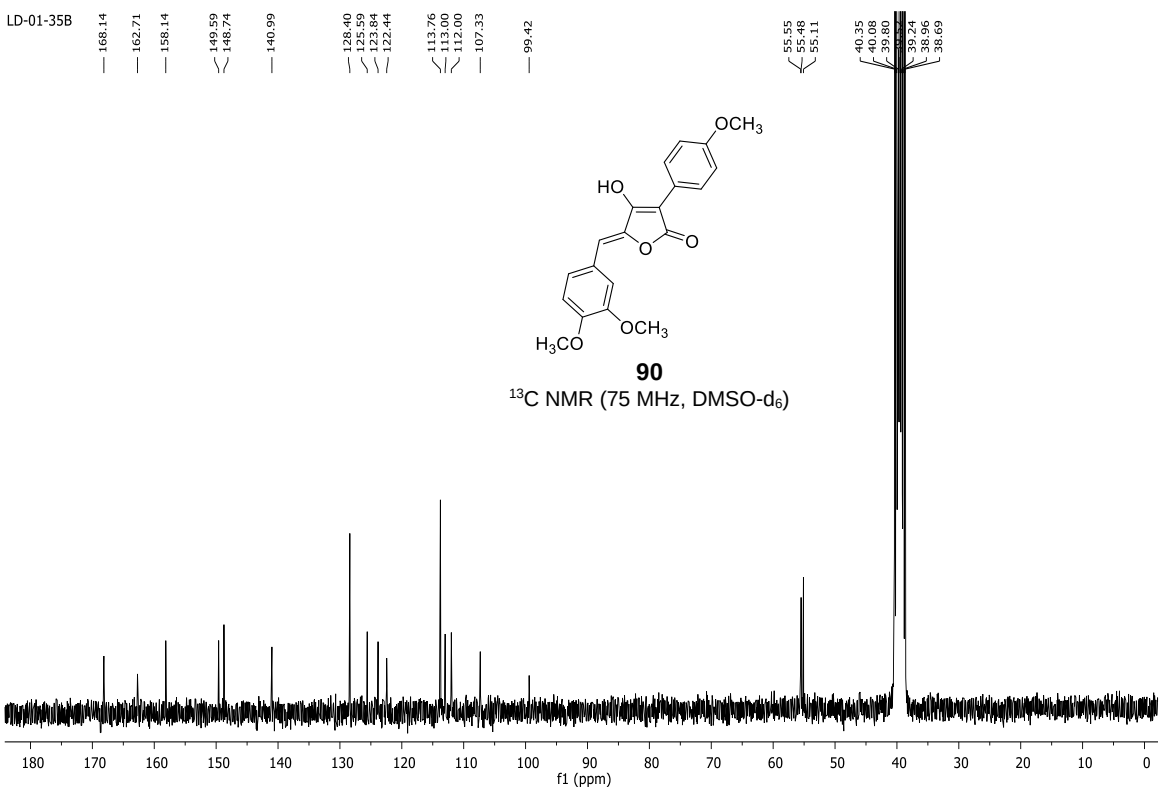
89

^{13}C NMR (75 MHz, $CDCl_3$)



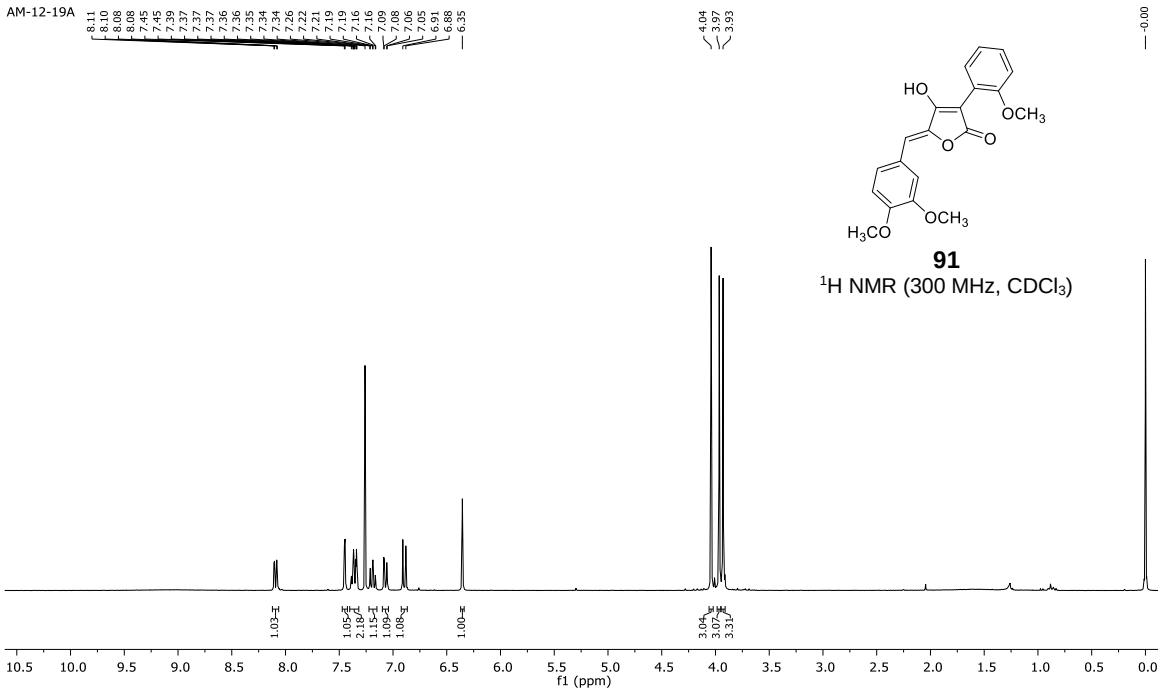
90

^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$, 97:3)



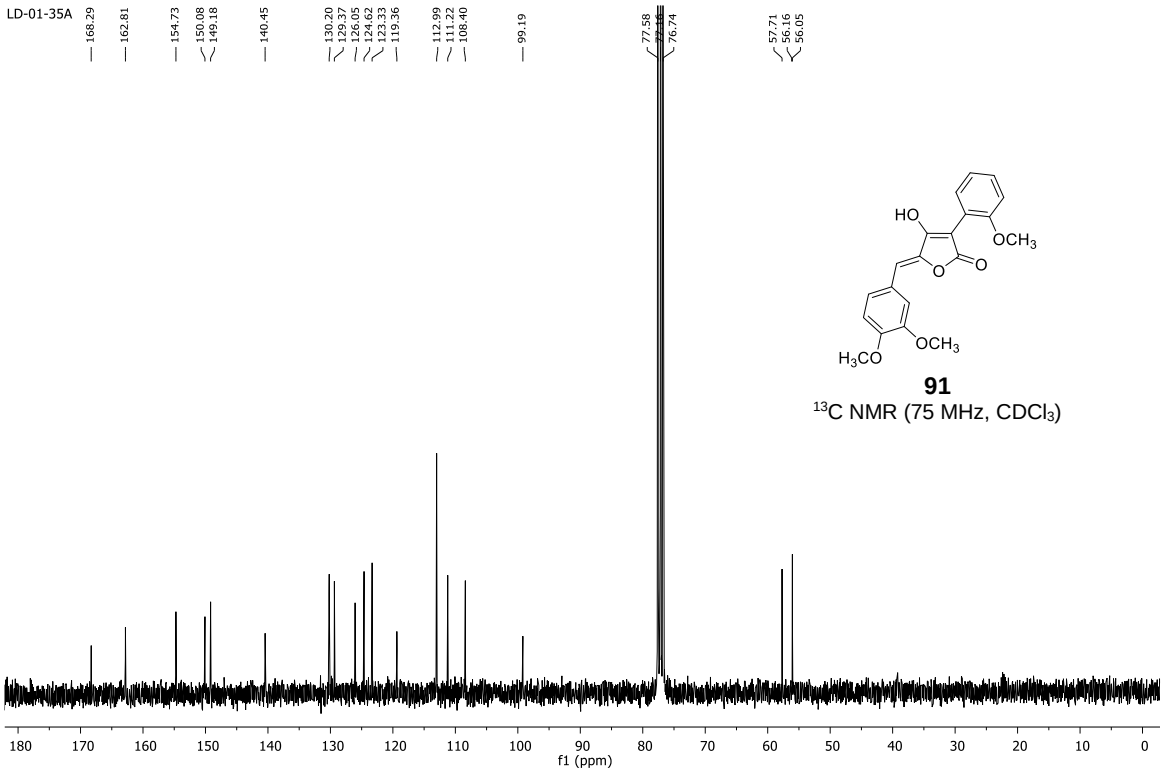
90

^{13}C NMR (75 MHz, DMSO-d_6)



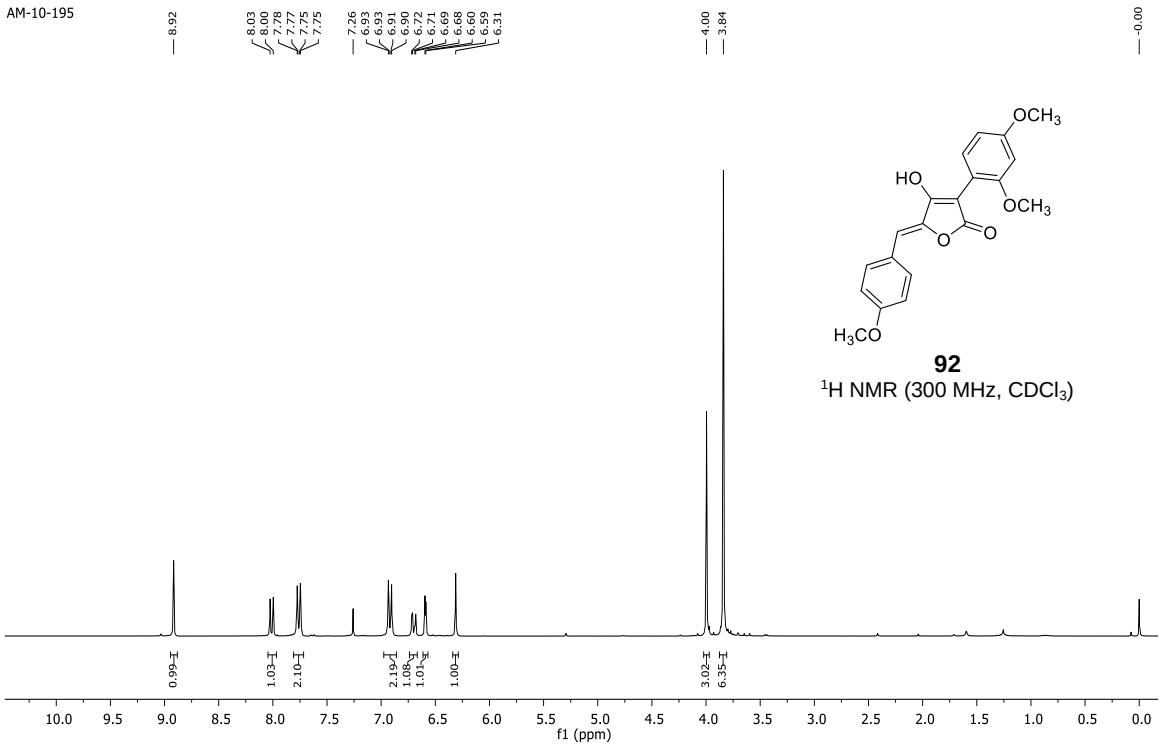
91

^{1}H NMR (300 MHz, $CDCl_3$)



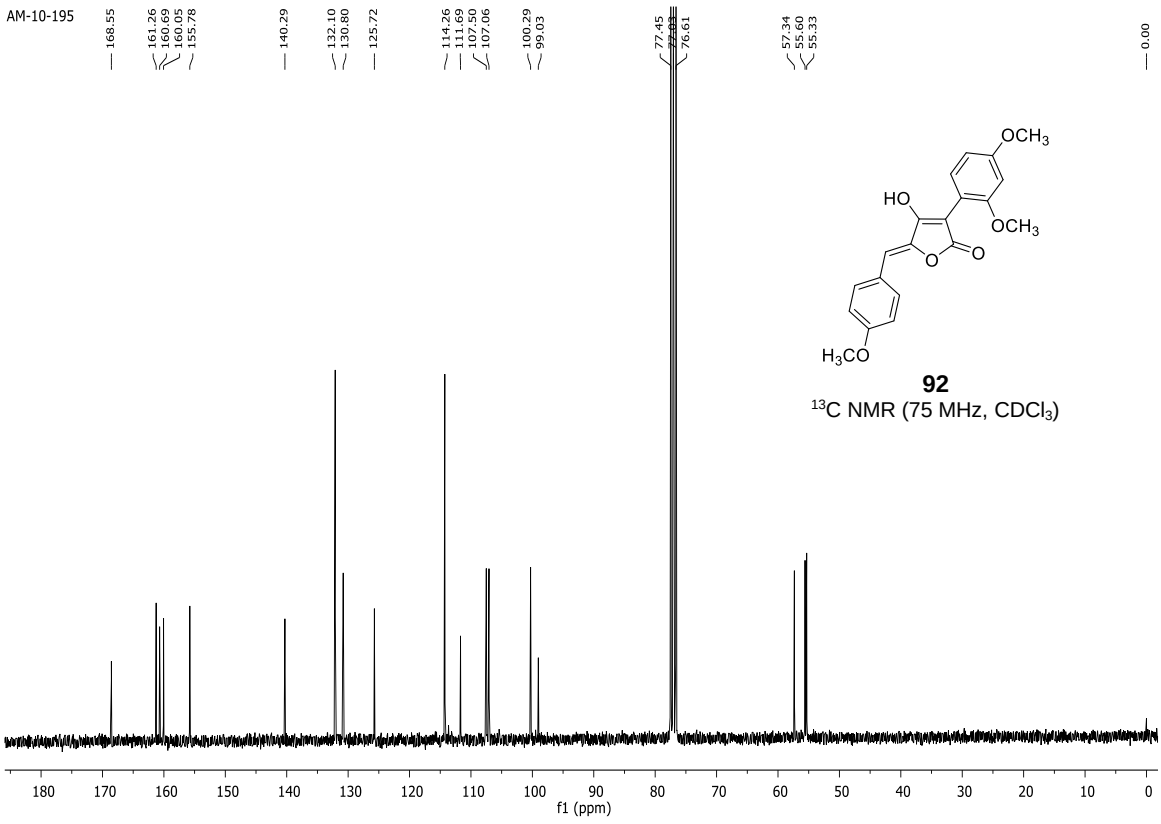
91

^{13}C NMR (75 MHz, $CDCl_3$)



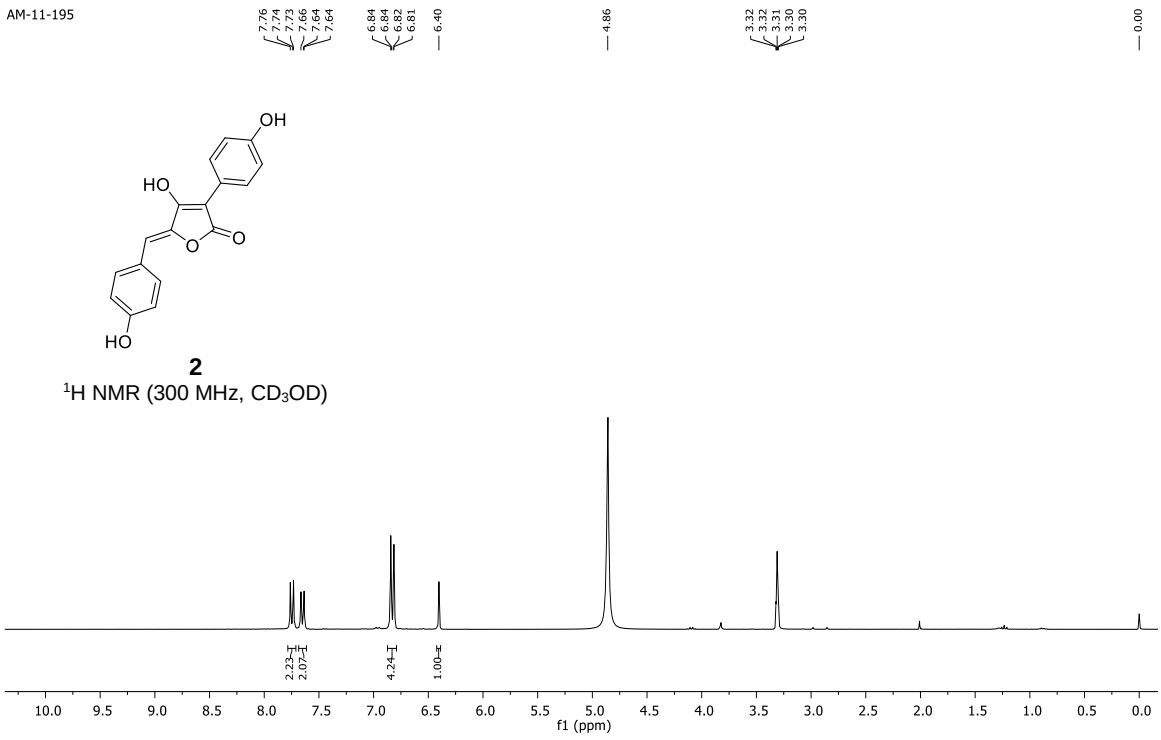
92

^{1}H NMR (300 MHz, $CDCl_3$)



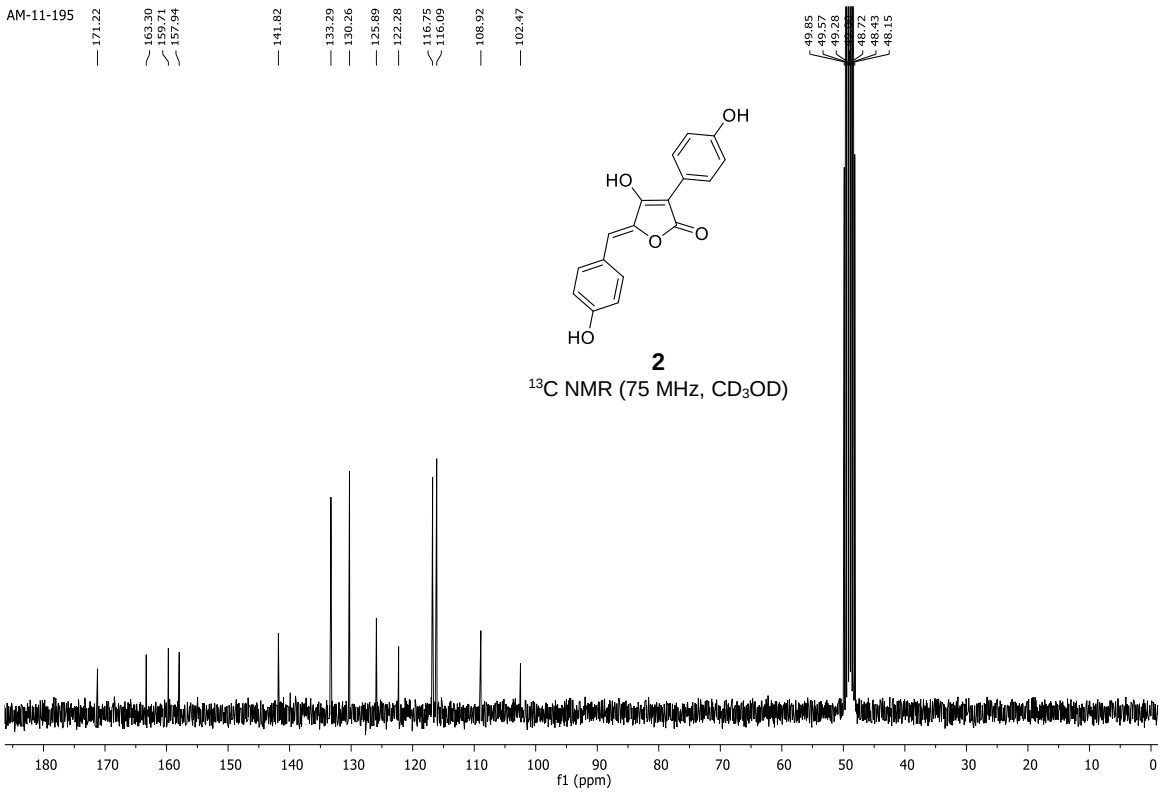
92

^{13}C NMR (75 MHz, $CDCl_3$)



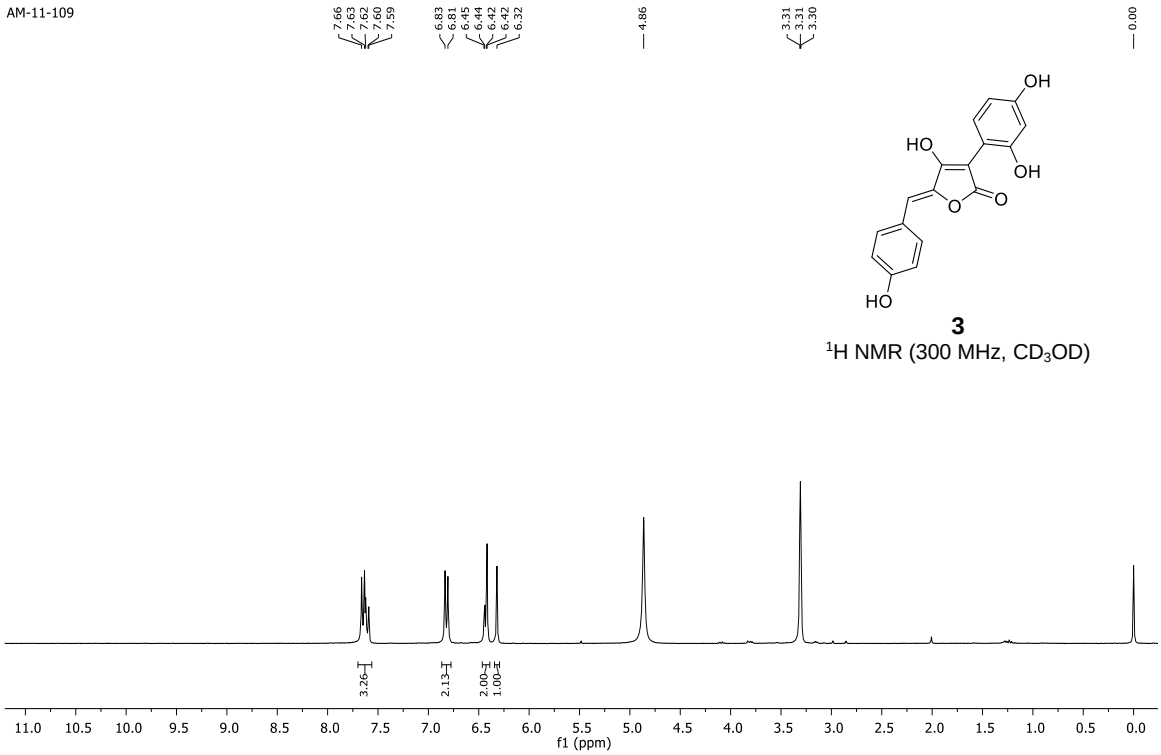
2

^{1}H NMR (300 MHz, CD_3OD)



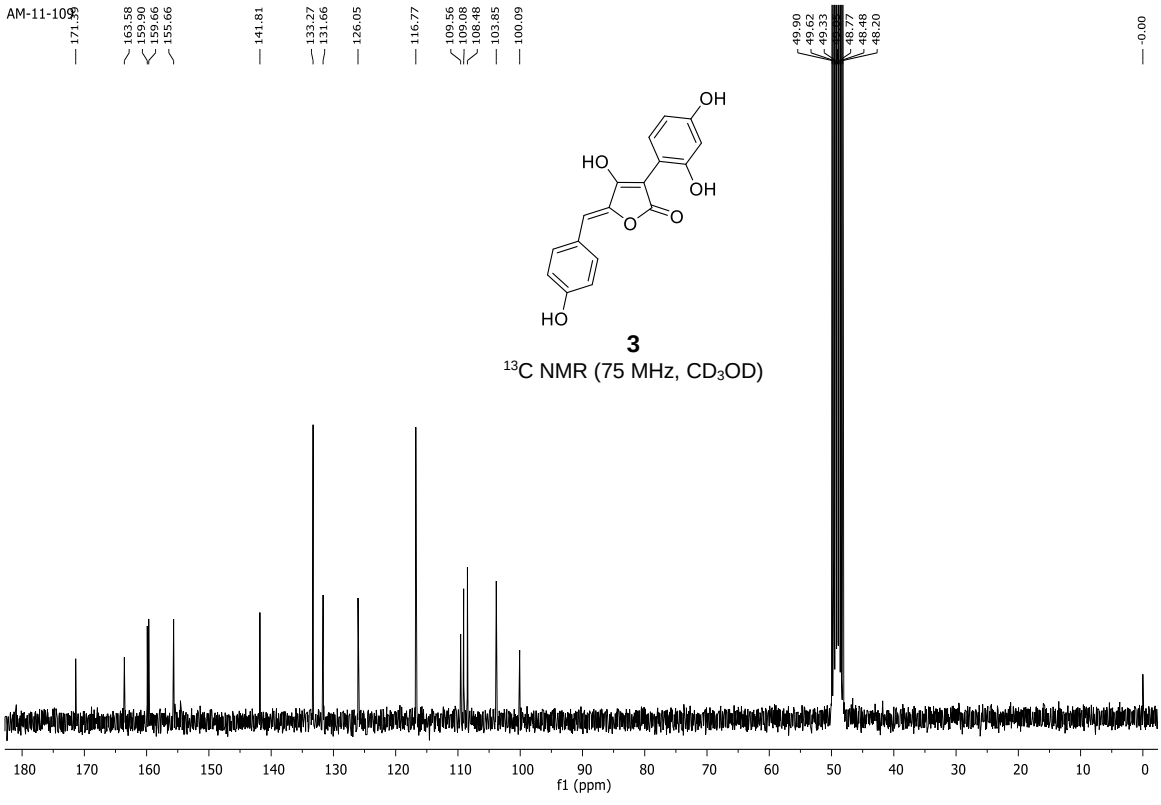
2

^{13}C NMR (75 MHz, CD_3OD)



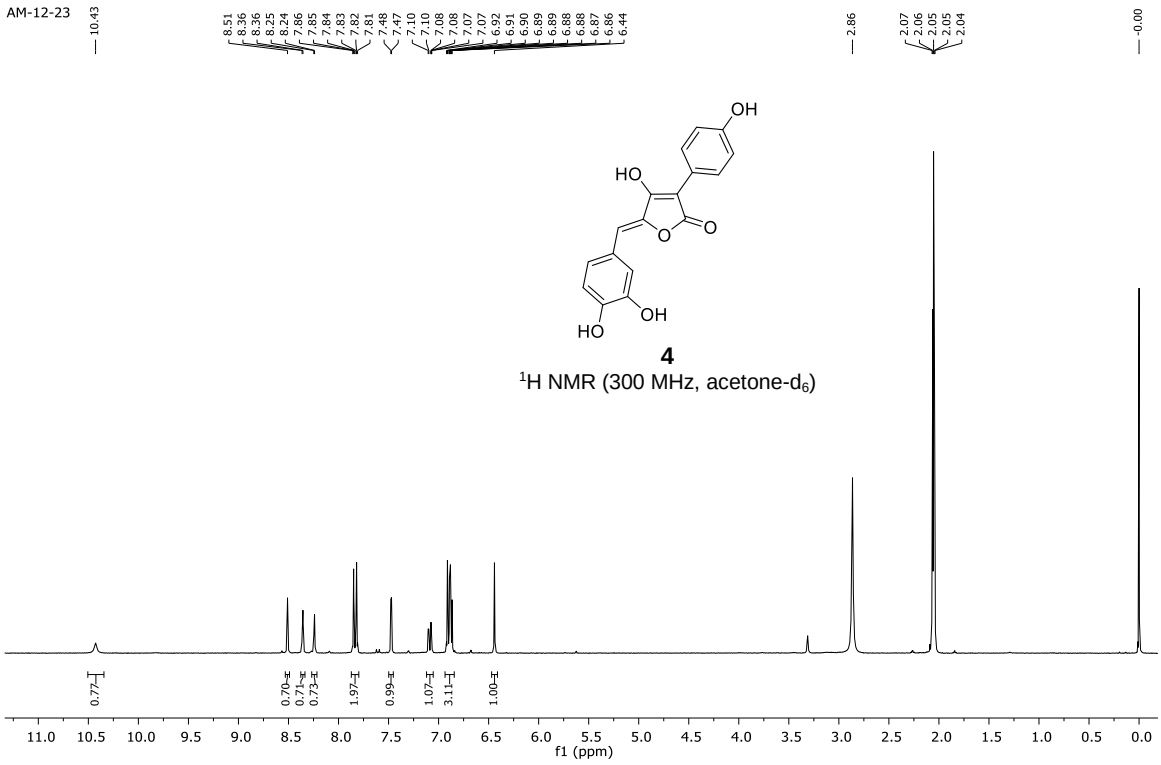
3

^{1}H NMR (300 MHz, CD_3OD)



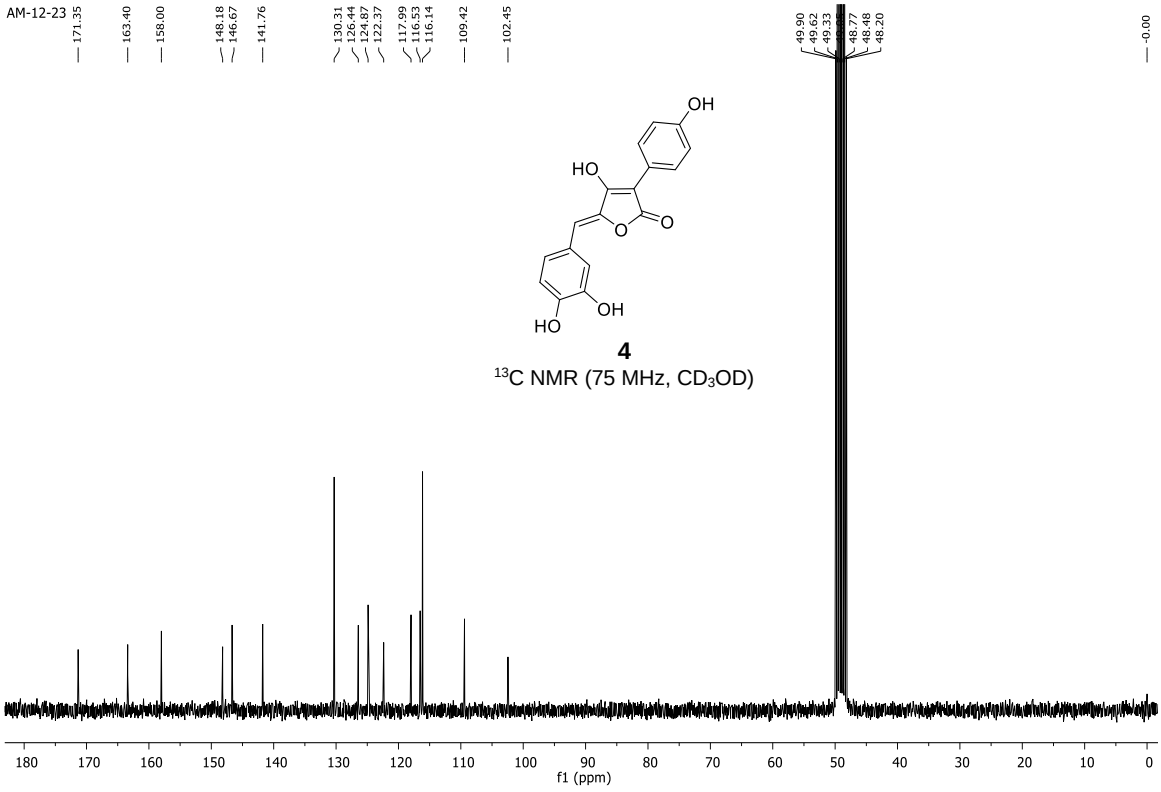
3

^{13}C NMR (75 MHz, CD_3OD)



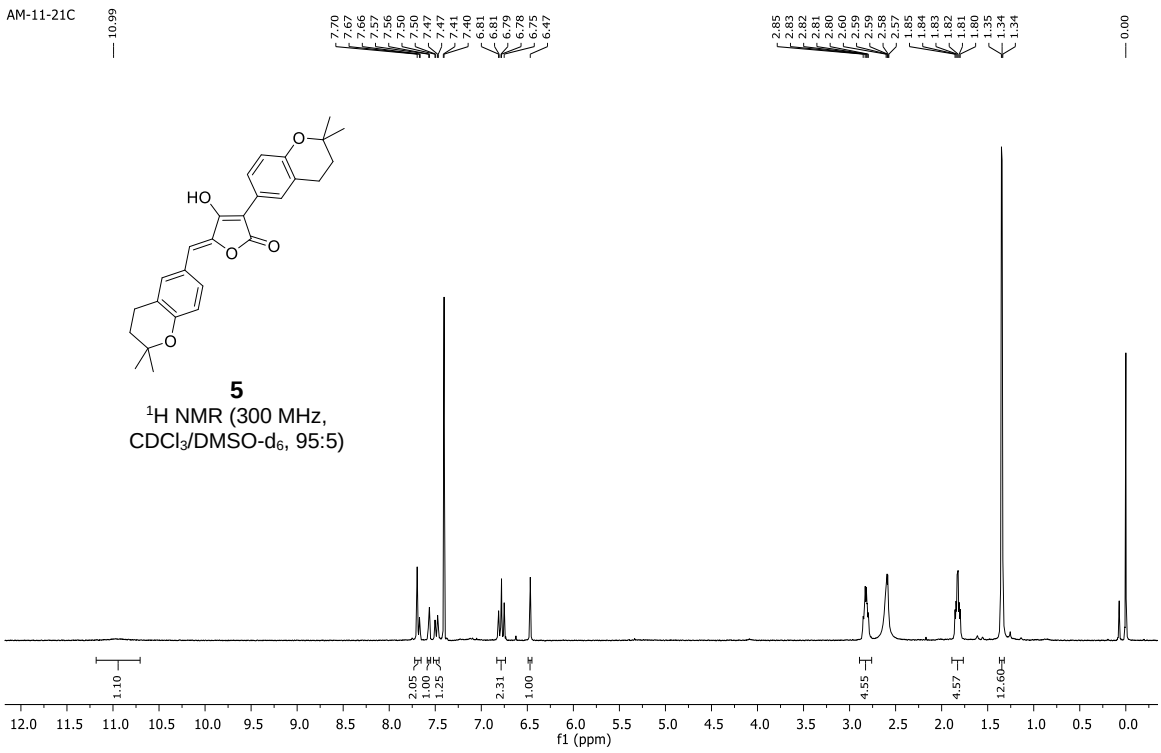
4

^{1}H NMR (300 MHz, acetone-d_6)



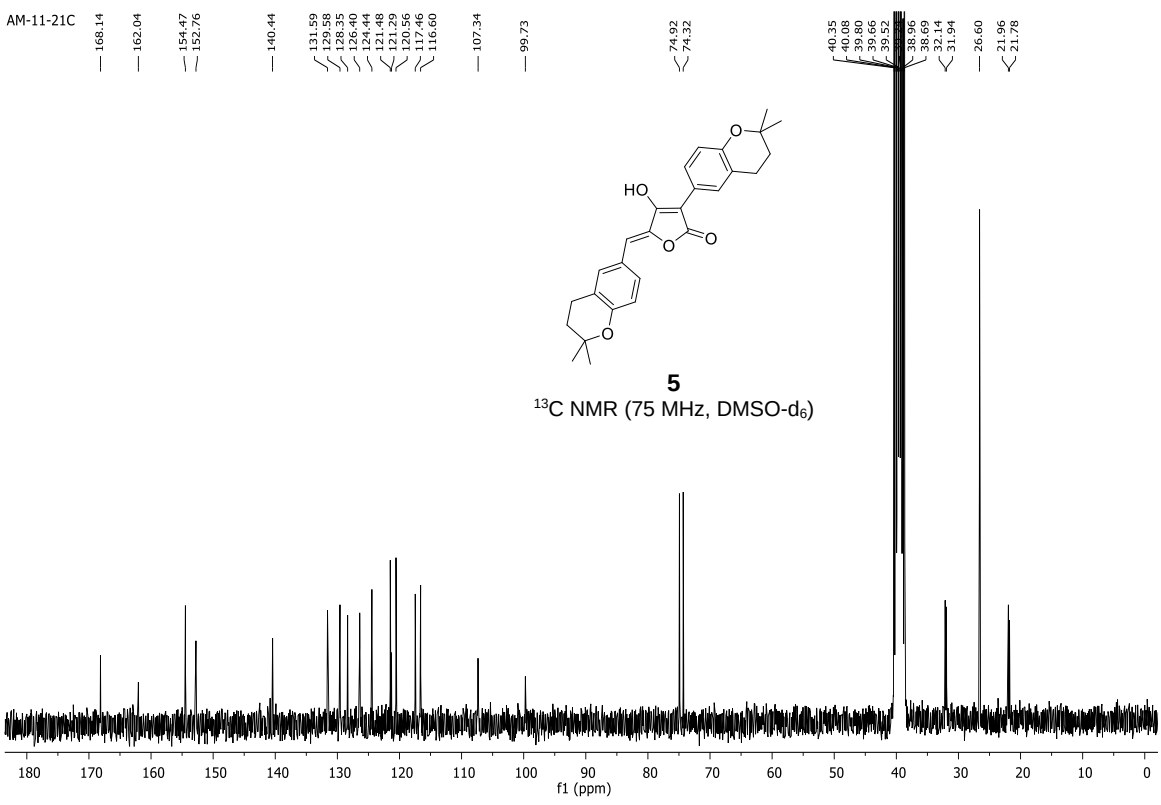
4

^{13}C NMR (75 MHz, CD_3OD)



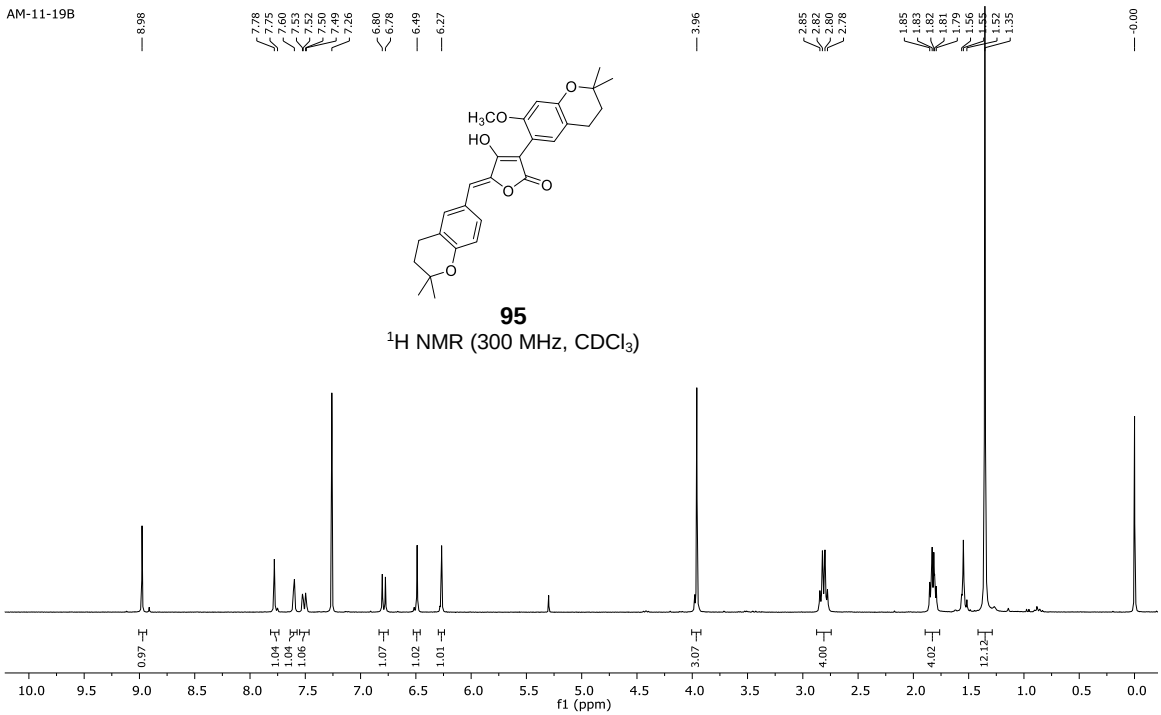
5

^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6, 95:5)



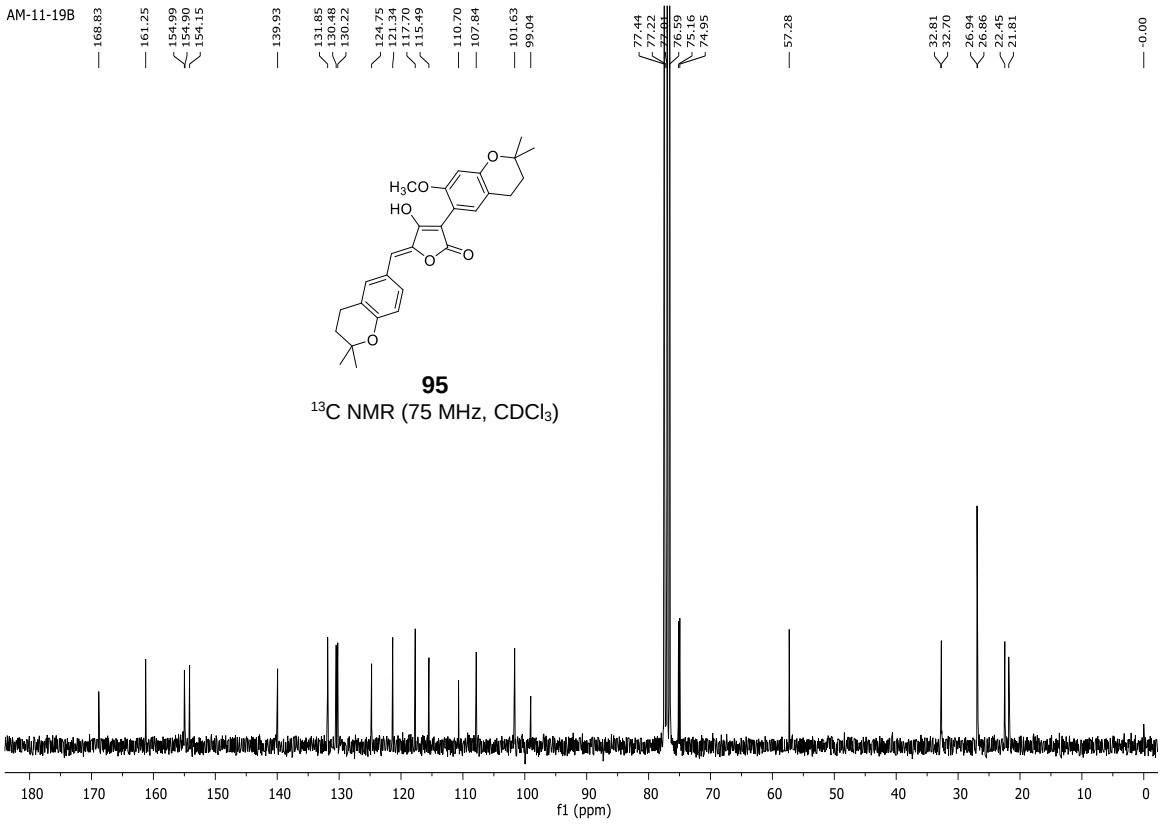
5

^{13}C NMR (75 MHz, DMSO-d_6)



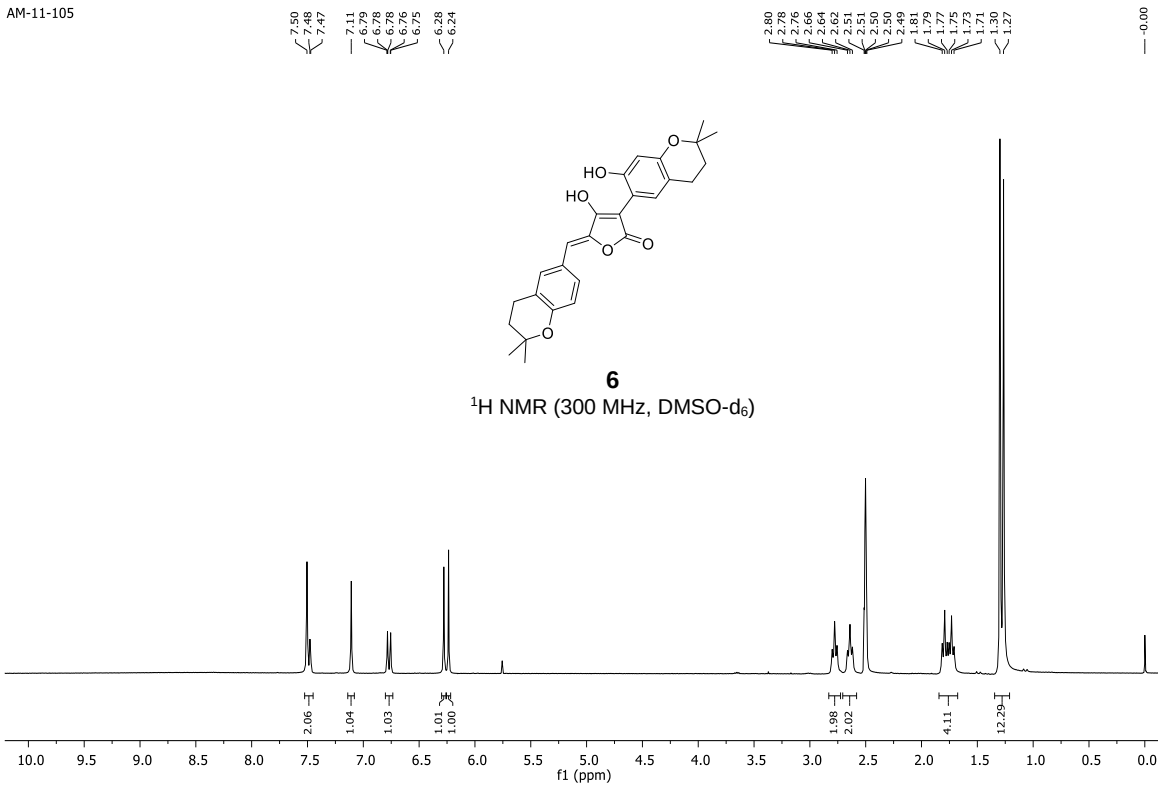
95

^{1}H NMR (300 MHz, $CDCl_3$)



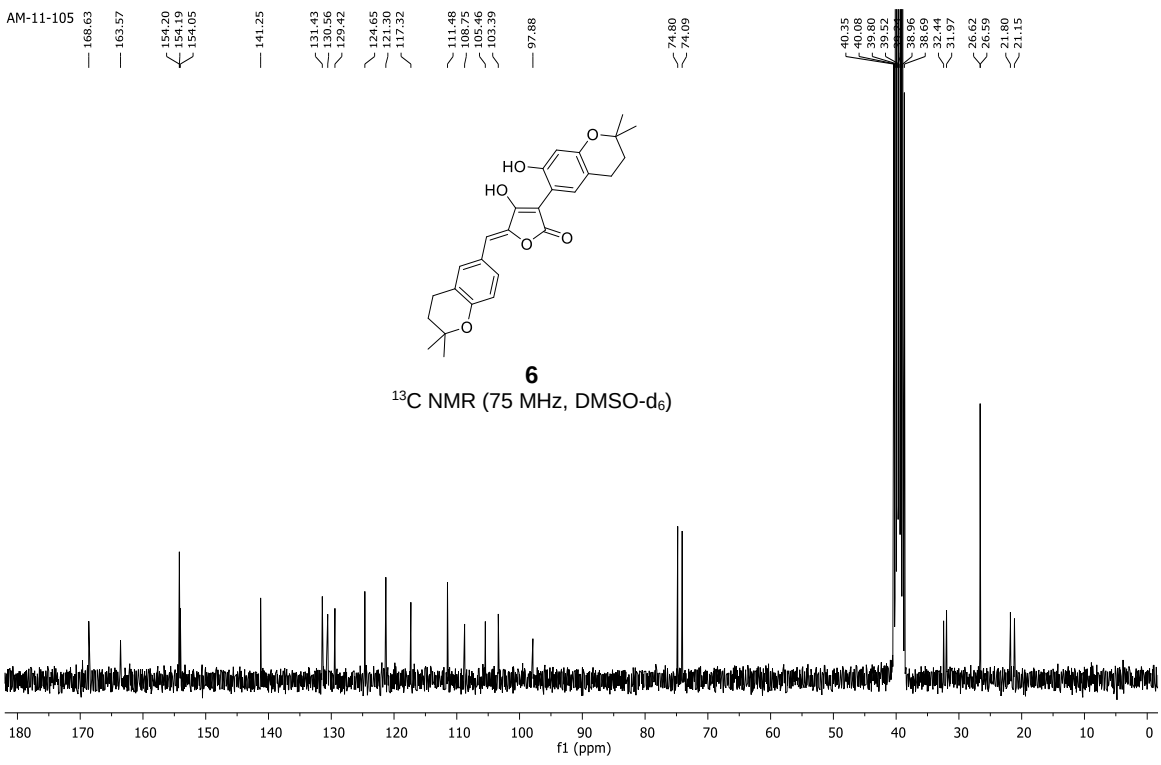
95

^{13}C NMR (75 MHz, $CDCl_3$)



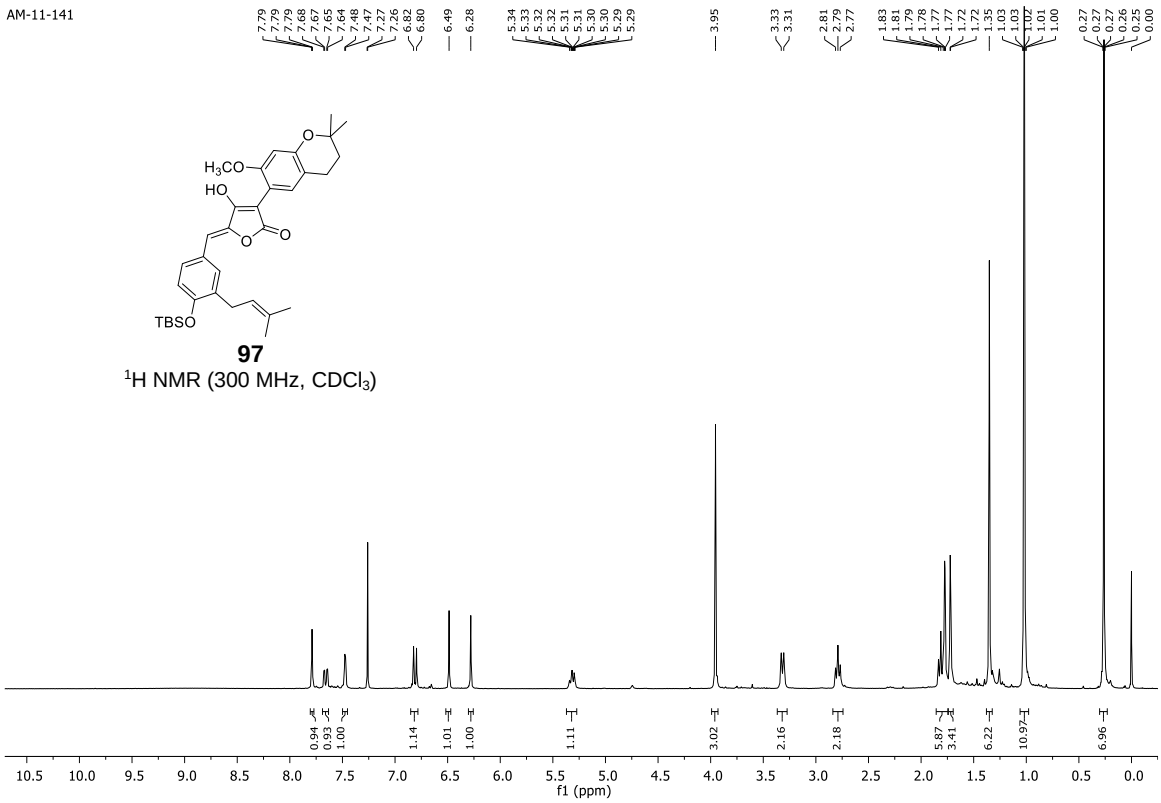
6

^{1}H NMR (300 MHz, DMSO-d_6)



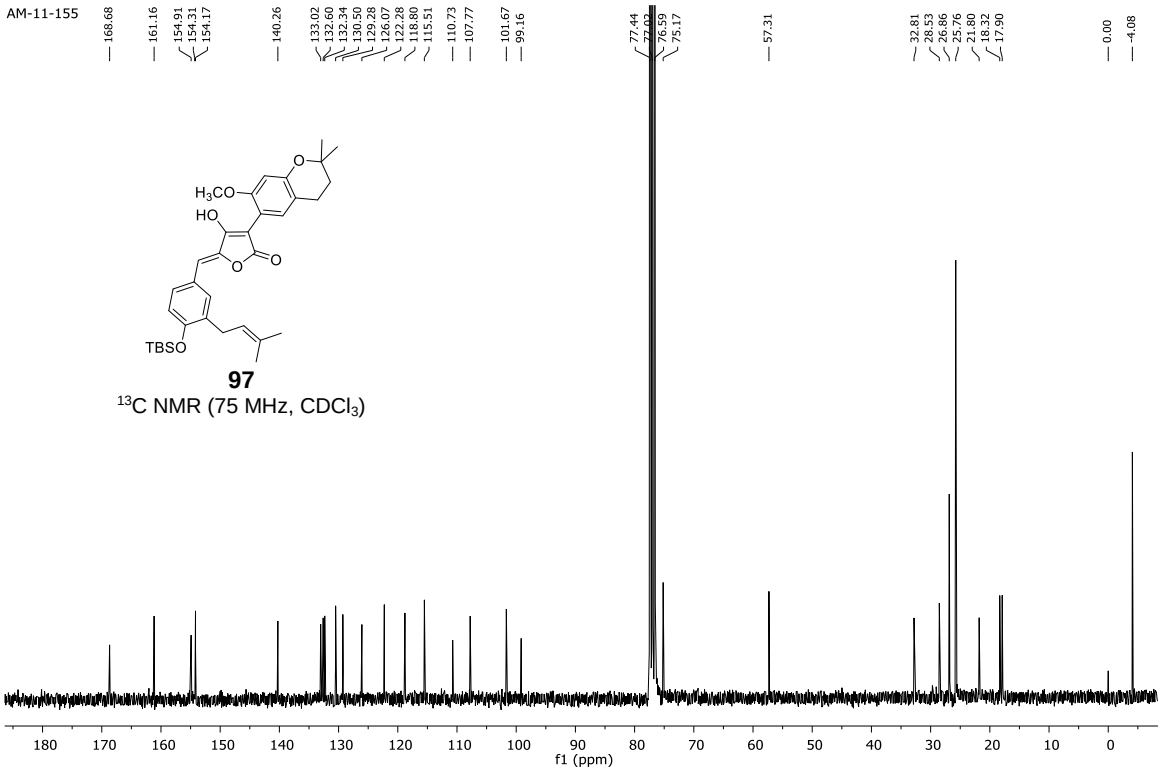
6

^{13}C NMR (75 MHz, DMSO-d_6)



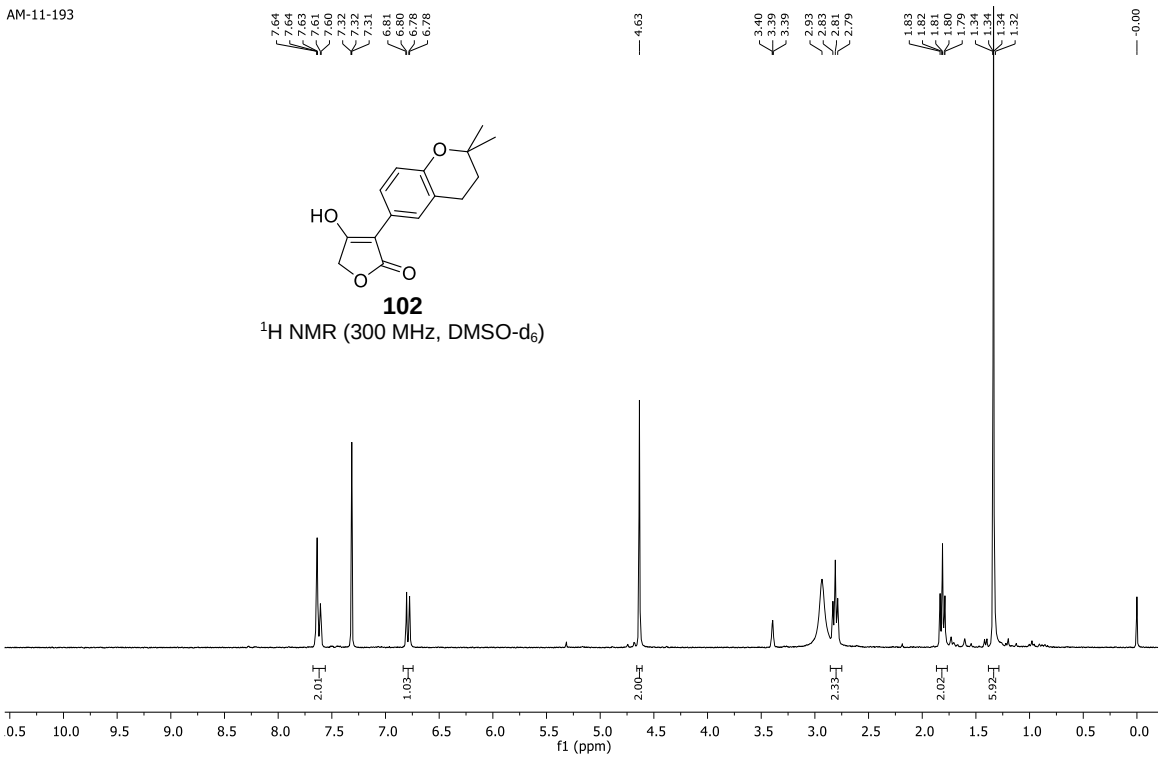
97

^{1}H NMR (300 MHz, $CDCl_3$)



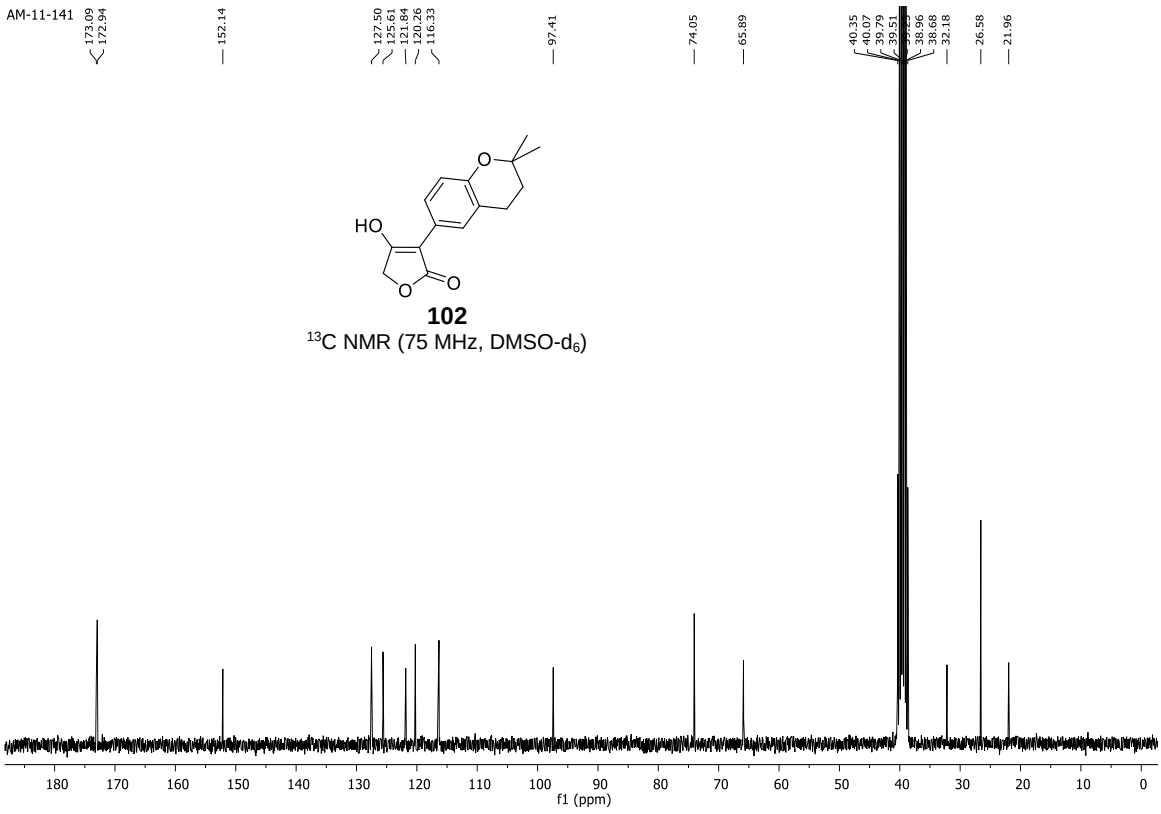
97

^{13}C NMR (75 MHz, $CDCl_3$)



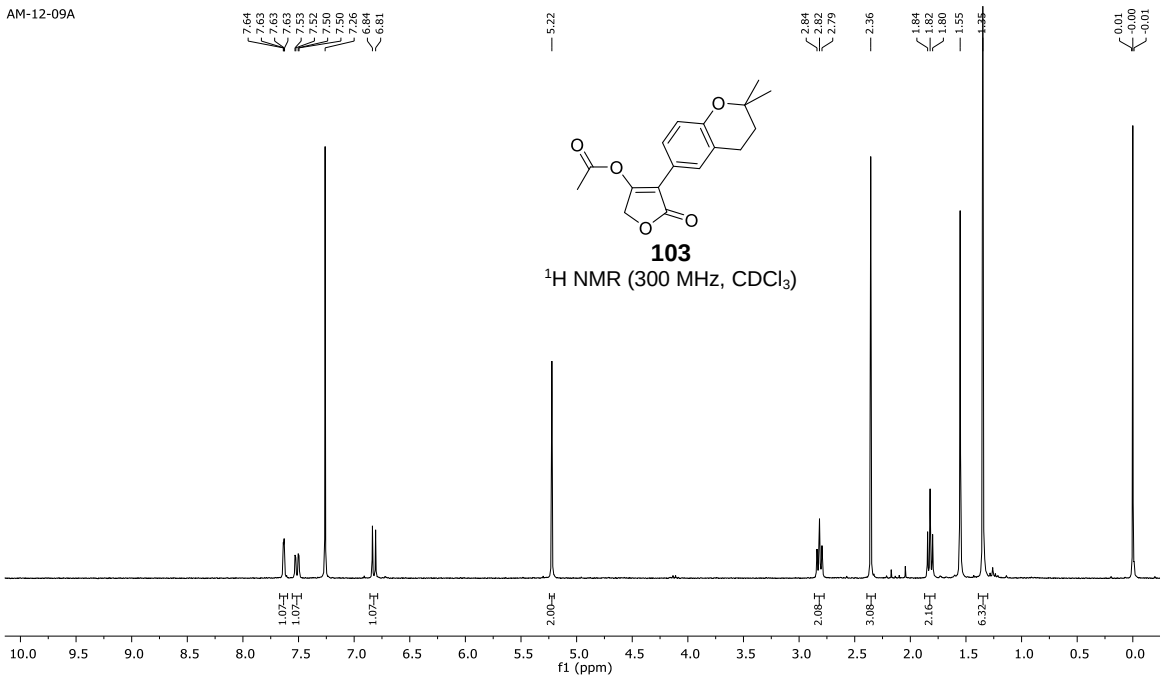
102

^{1}H NMR (300 MHz, DMSO-d_6)



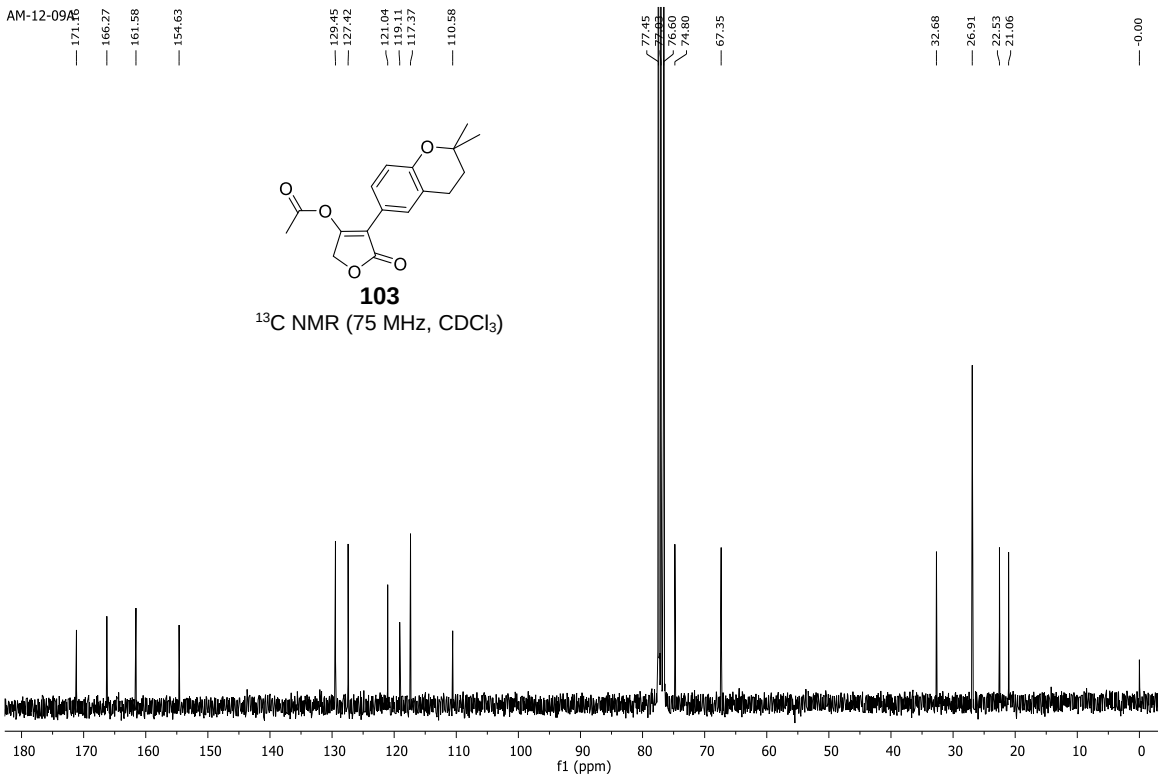
102

^{13}C NMR (75 MHz, DMSO-d_6)



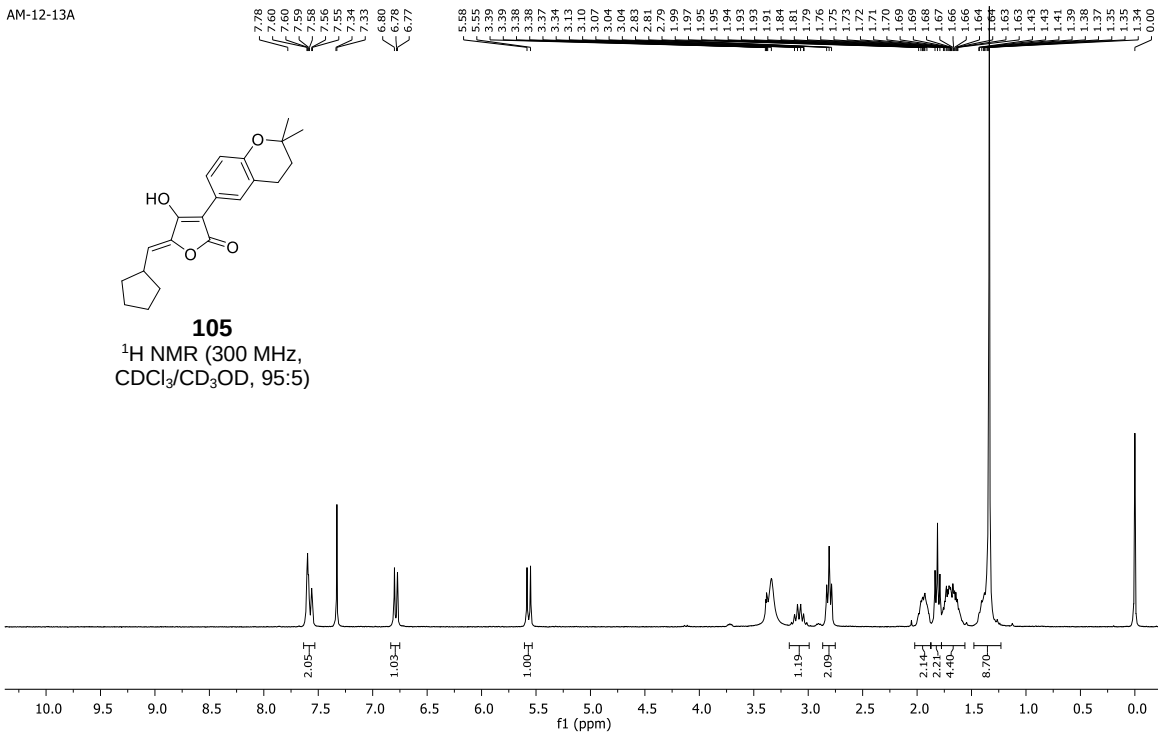
103

^{1}H NMR (300 MHz, $CDCl_3$)

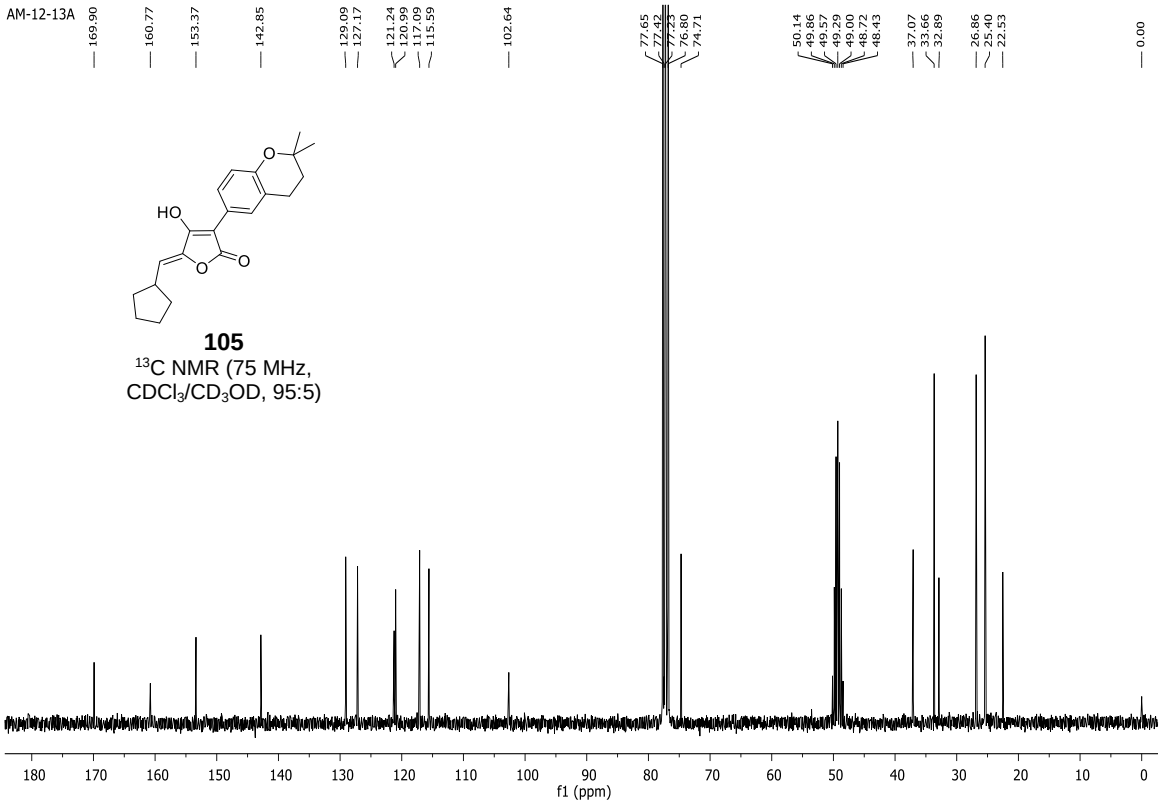


103

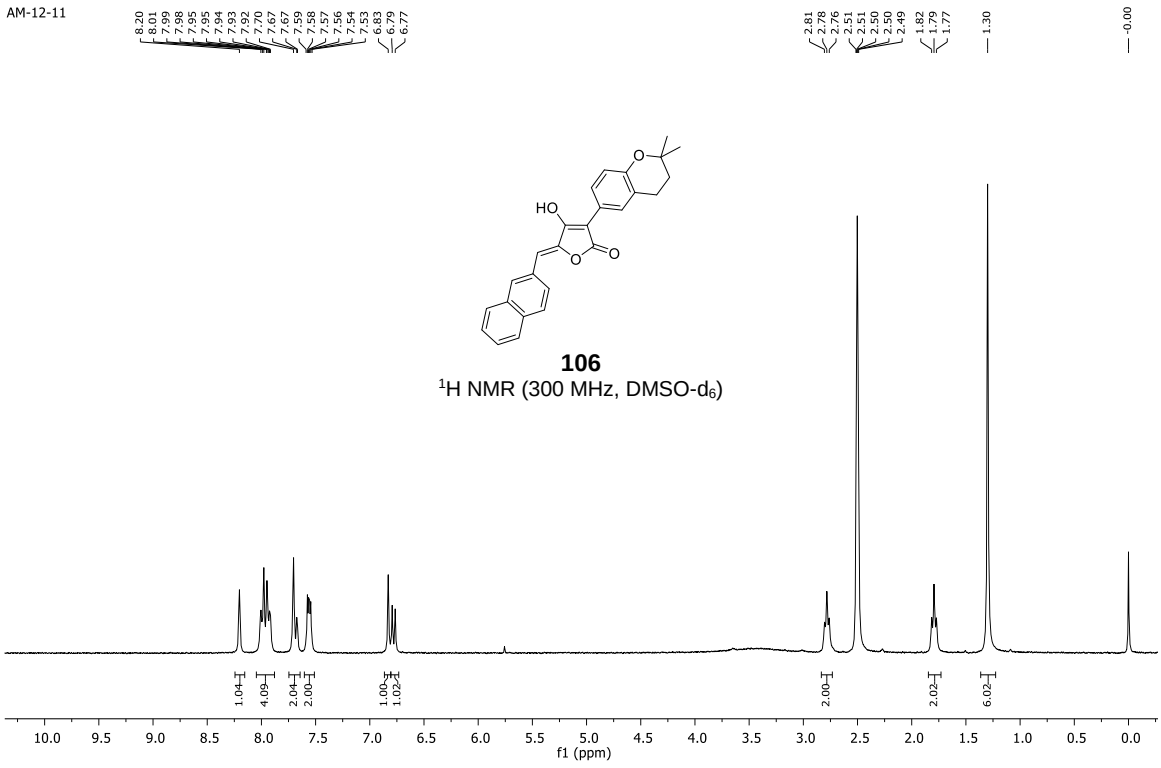
^{13}C NMR (75 MHz, $CDCl_3$)



105
^{1}H NMR (300 MHz,
$CDCl_3/CD_3OD$, 95:5)

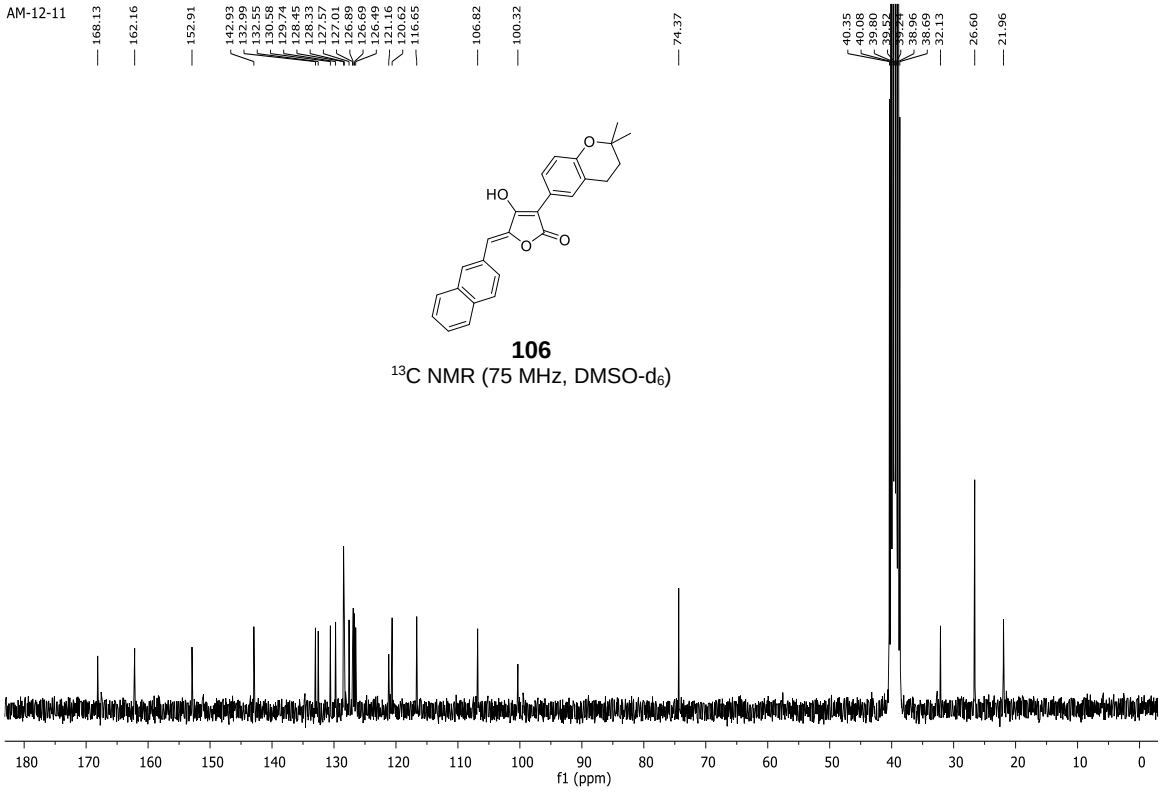


105
^{13}C NMR (75 MHz,
$CDCl_3/CD_3OD$, 95:5)



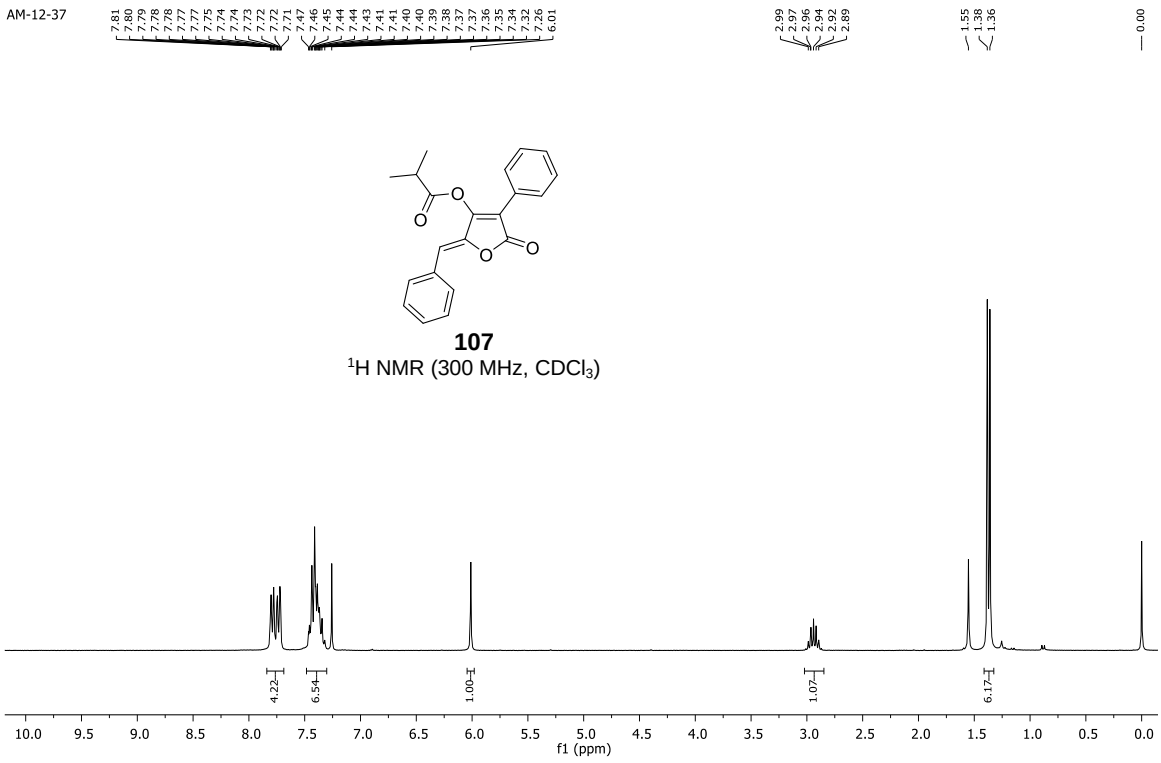
106

^{1}H NMR (300 MHz, DMSO-d_6)



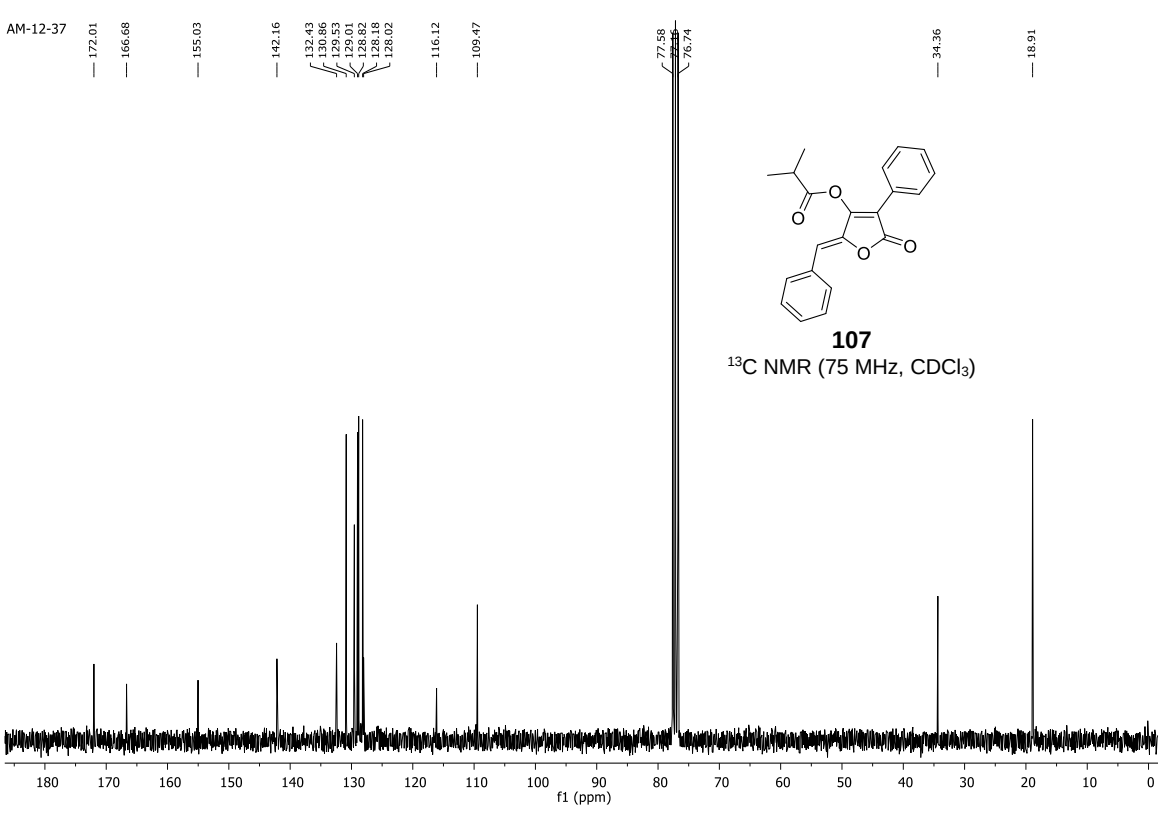
106

^{13}C NMR (75 MHz, DMSO-d_6)



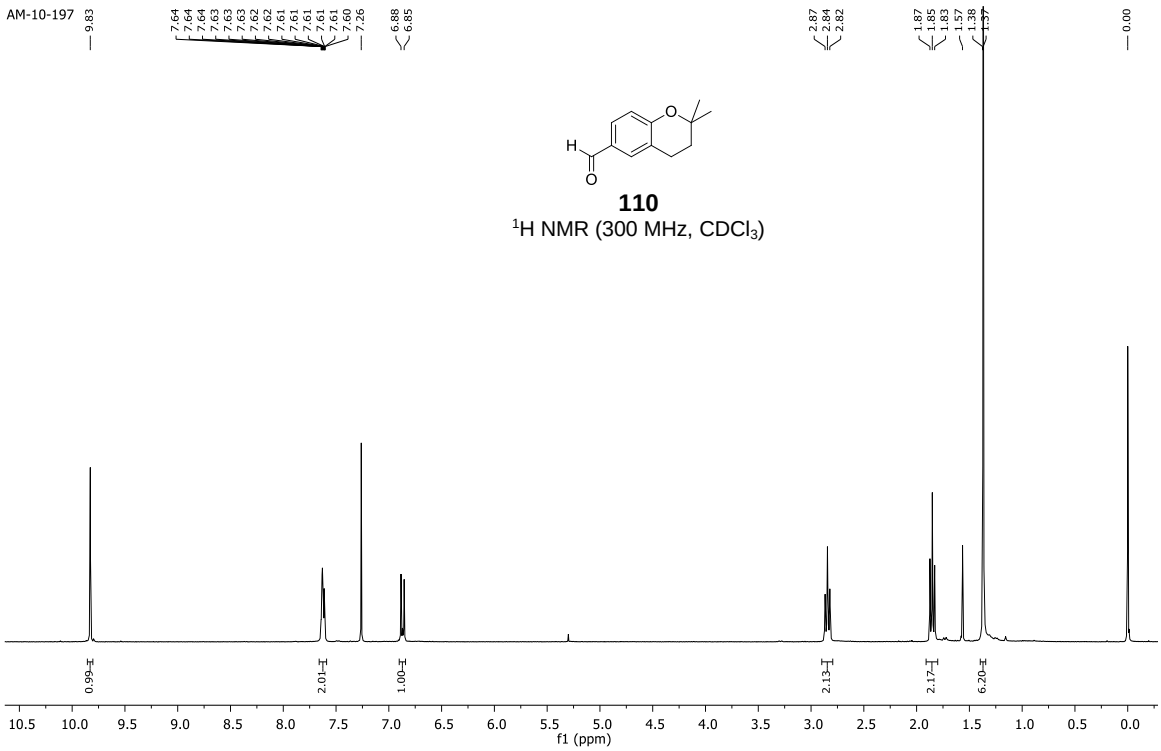
107

^{1}H NMR (300 MHz, $CDCl_3$)



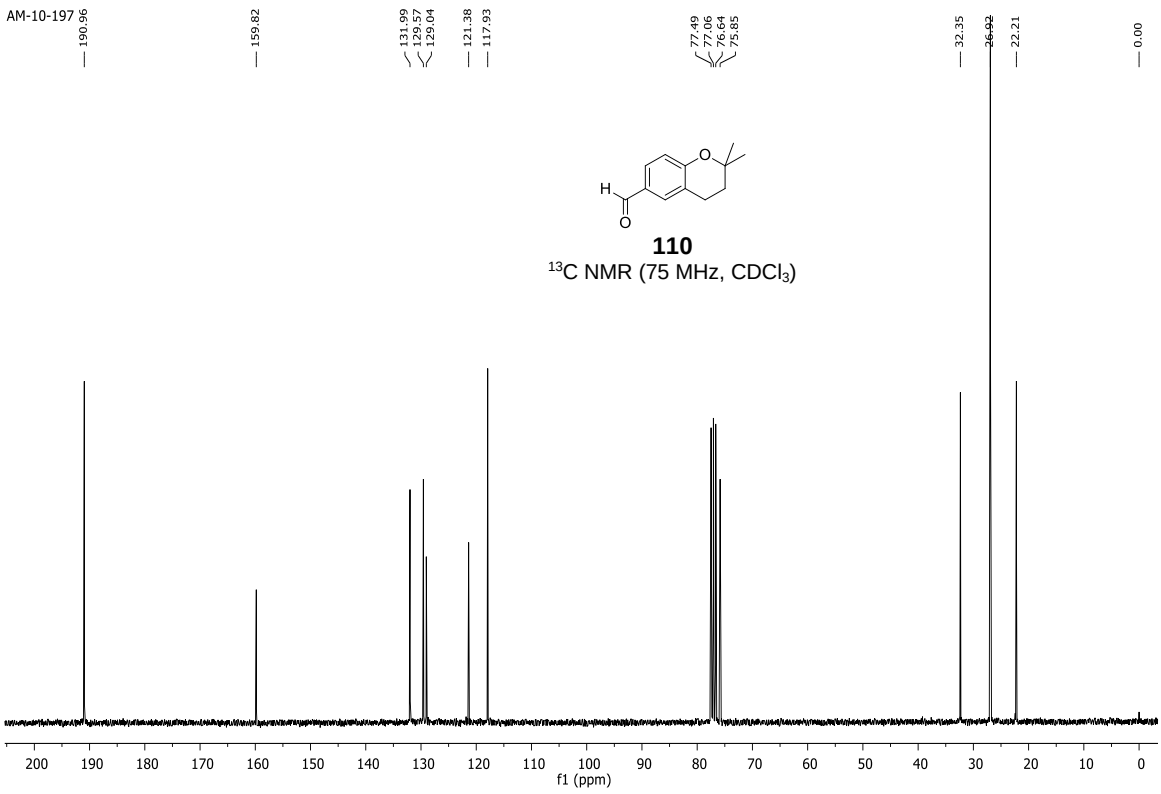
107

^{13}C NMR (75 MHz, $CDCl_3$)



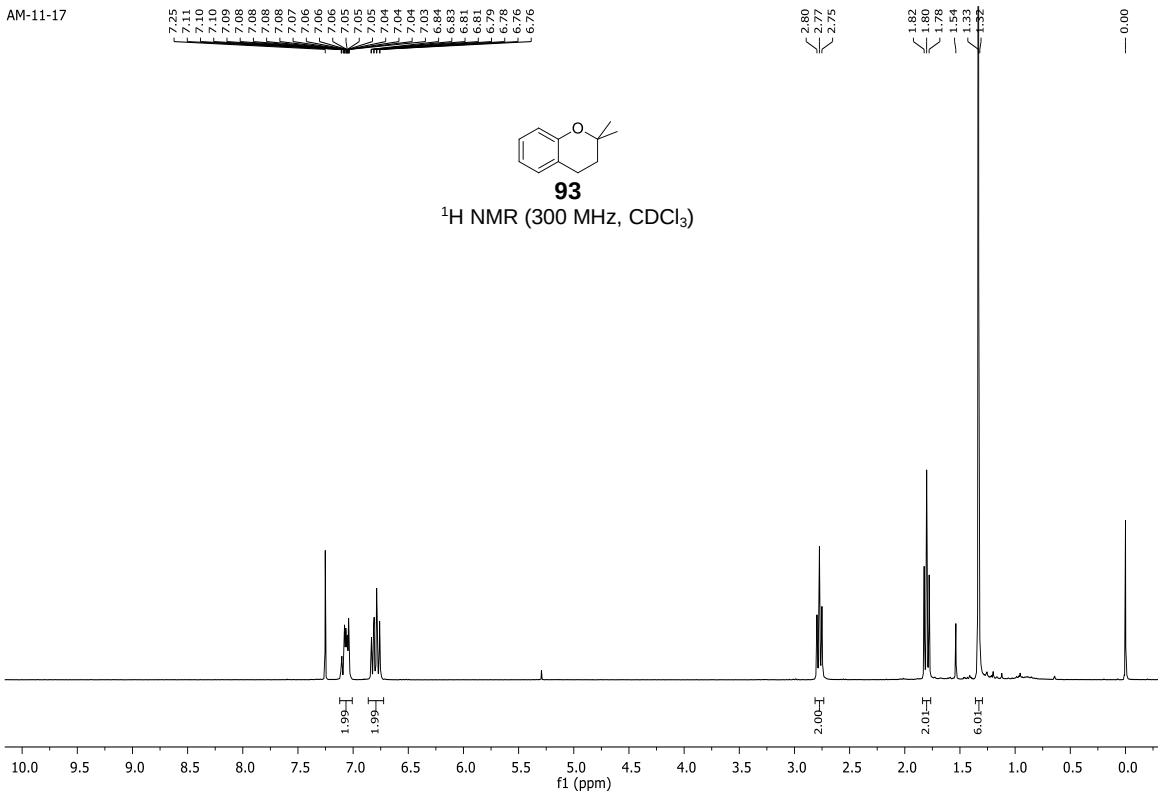
110

^{1}H NMR (300 MHz, $CDCl_3$)



110

^{13}C NMR (75 MHz, $CDCl_3$)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1.32
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O
93
1H NMR (300 MHz, CDCl3)
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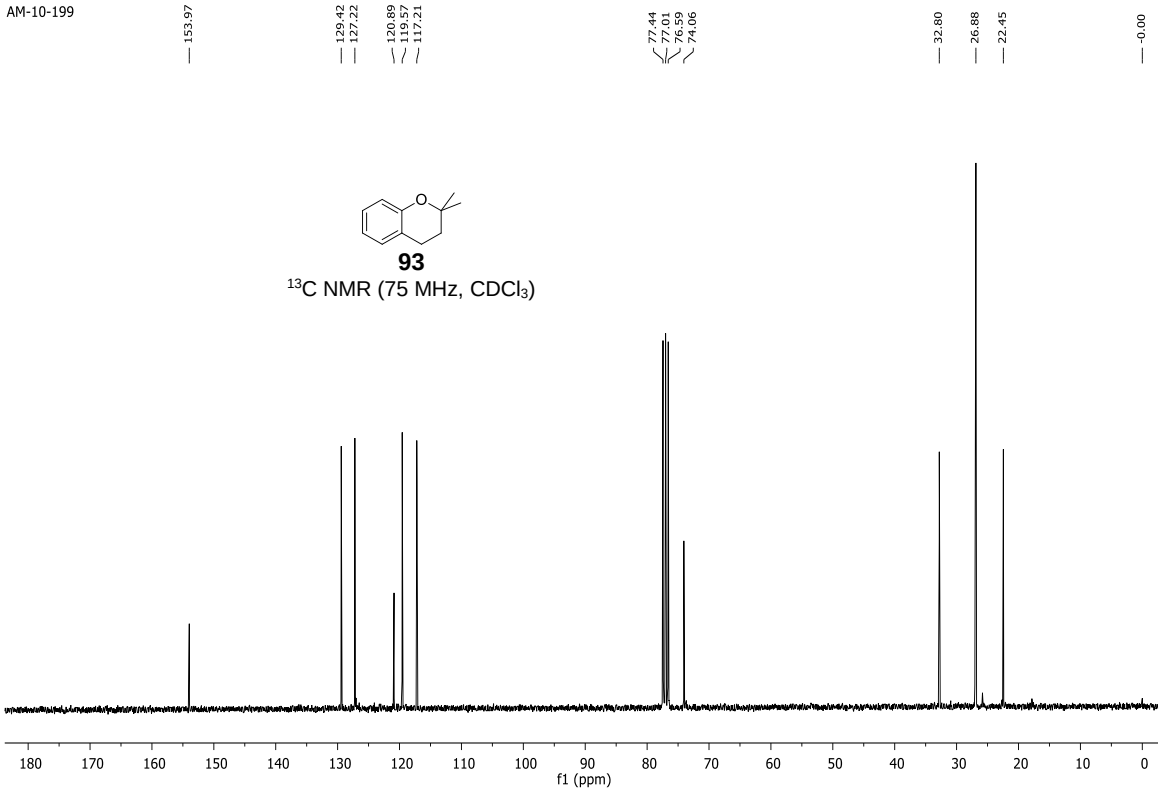
1.99
2.00
2.01
6.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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77.01
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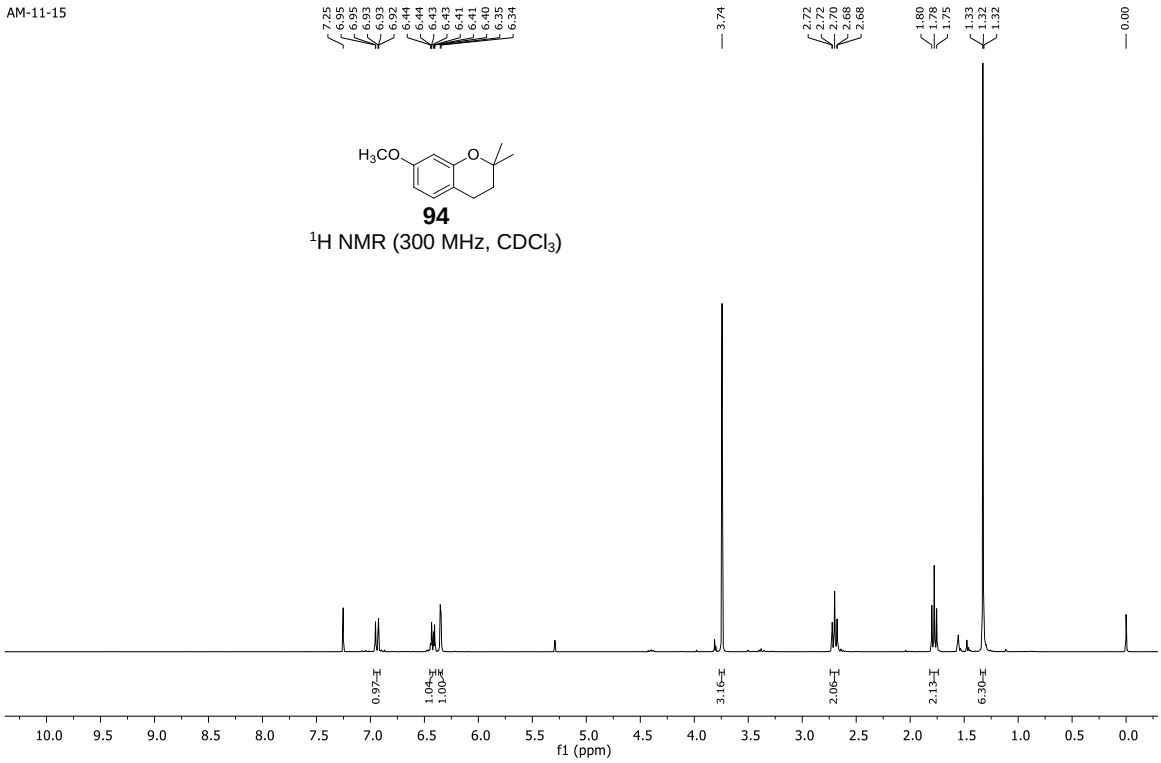
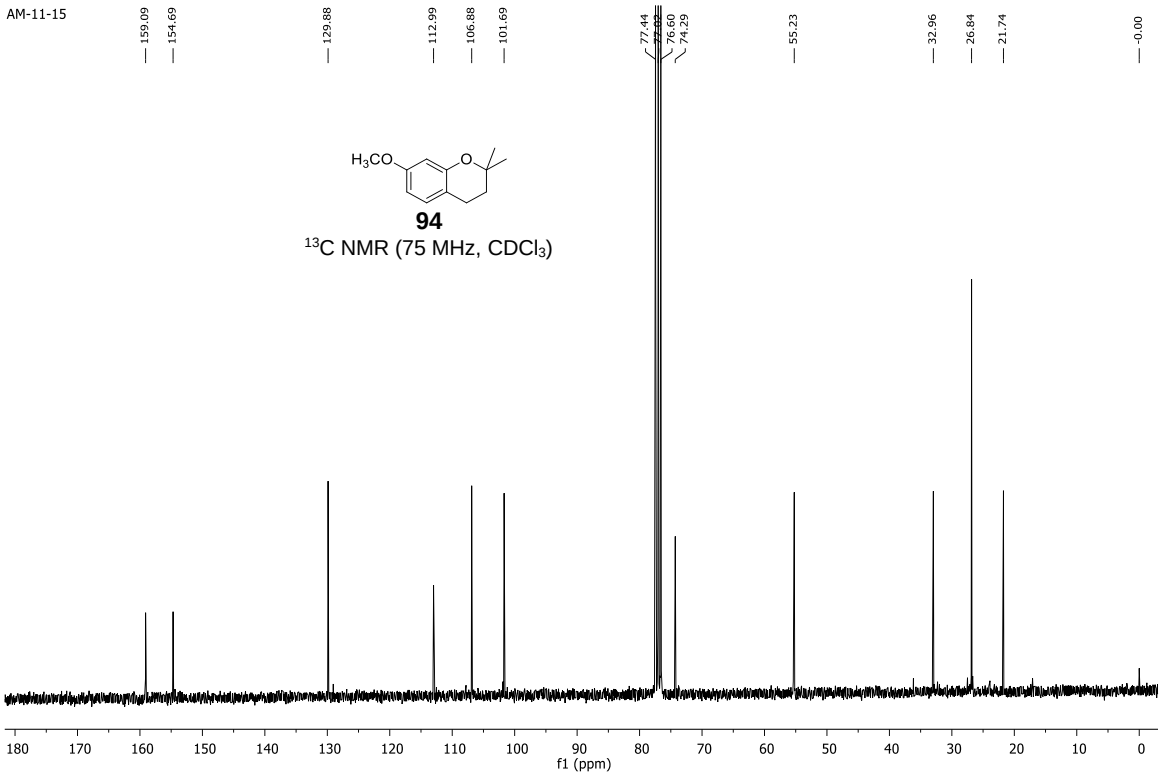
74.06
32.80
26.88
22.45
-0.00
O
93
13C NMR (75 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


AM-11-15
7.25
6.95
6.95
6.93
6.93
6.92
6.44
6.44
6.43
6.43
6.41
6.41
6.40
6.35
6.34
3.74
2.72
2.72
2.70
2.68
2.68
1.80
1.78
1.75
1.33
1.32
1.32
0.00
H3CO
O
94
1H NMR (300 MHz, CDCl3)
0.97
1.04
1.00
3.16
2.06
2.13
6.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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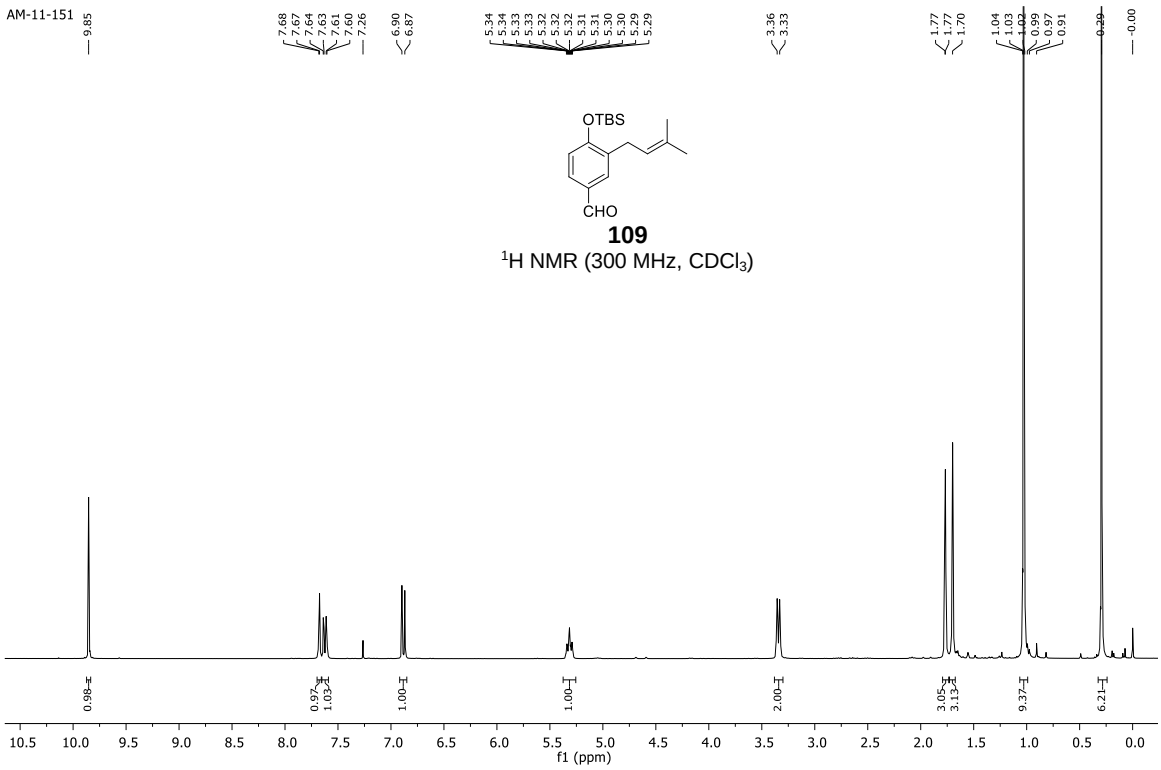
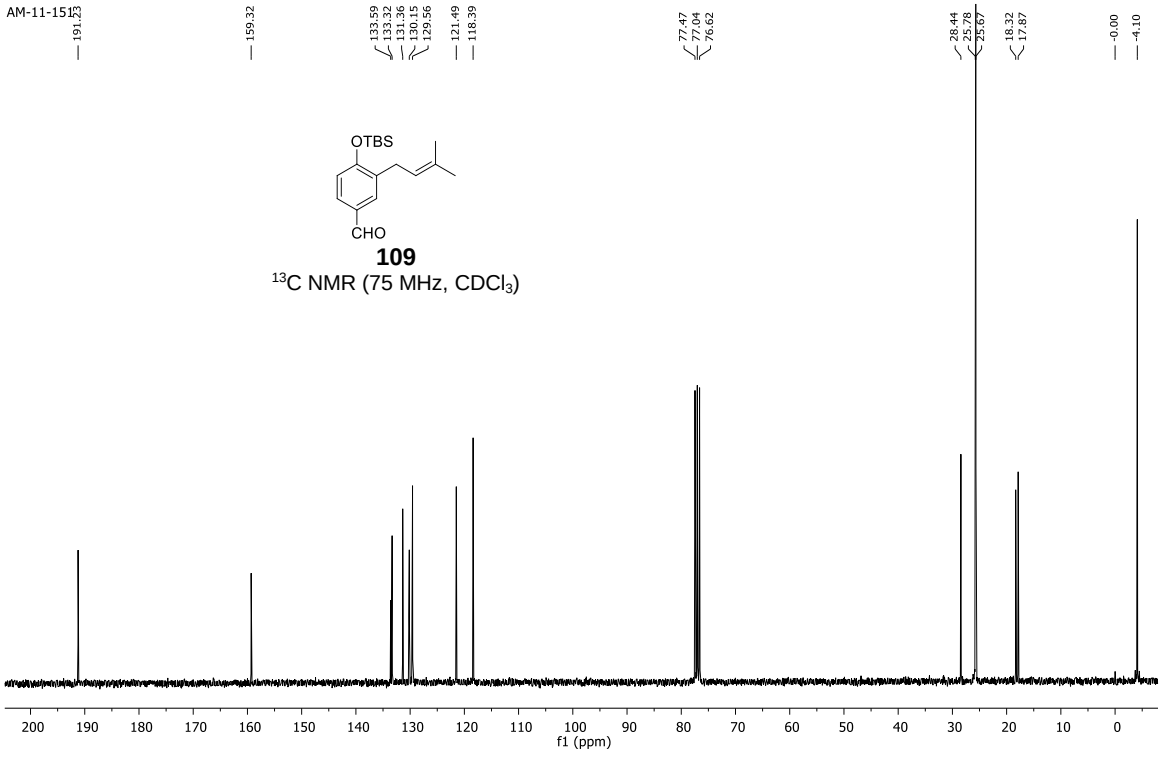
129.88
112.99
106.88
101.69
77.44
77.02
76.60
74.29
55.23
32.96
26.84
21.74
-0.00
H3CO
O
94
13C NMR (75 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



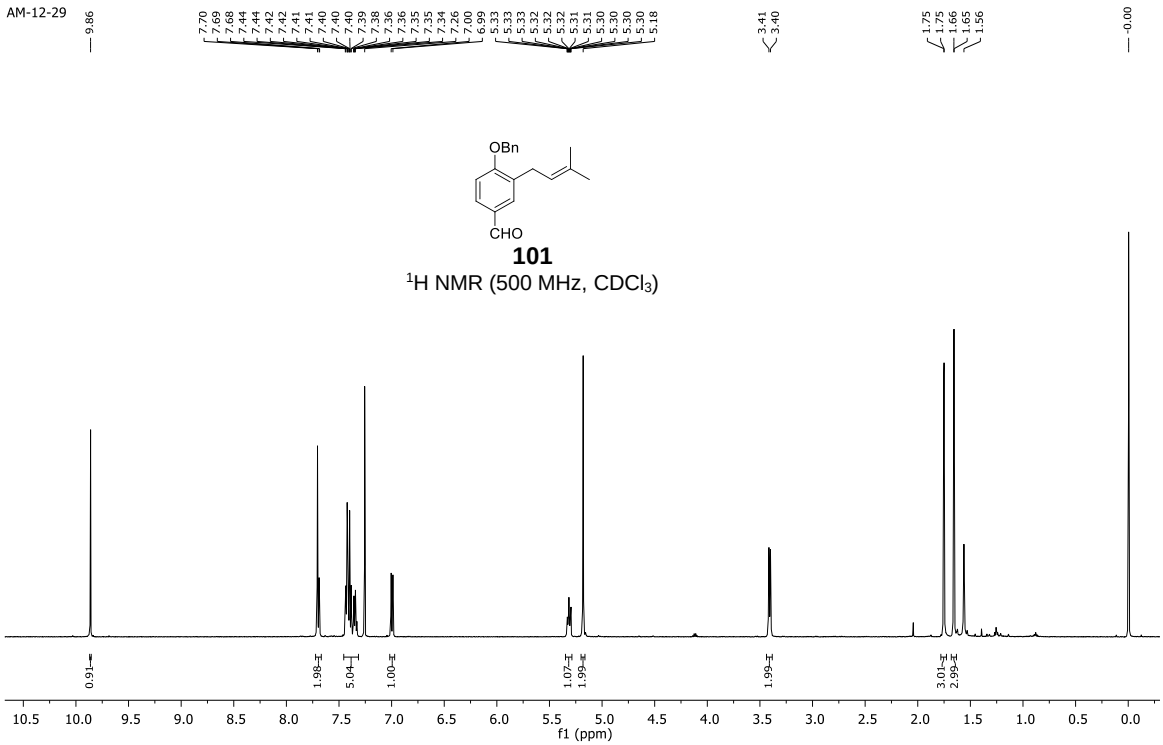
109

^{1}H NMR (300 MHz, $CDCl_3$)



109

^{13}C NMR (75 MHz, $CDCl_3$)


AM-12-29
9.86
7.70
7.69
7.68
7.44
7.44
7.42
7.42
7.41
7.41
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7.39
7.38
7.36
7.36
7.35
7.35
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6.99
5.33
5.33
5.32
5.32
5.32
5.31
5.31
5.30
5.30
5.30
5.30
5.18
3.41
3.40
1.75
1.75
1.66
1.65
1.56
0.00
OBn
CHO
101
1H NMR (500 MHz, CDCl3)
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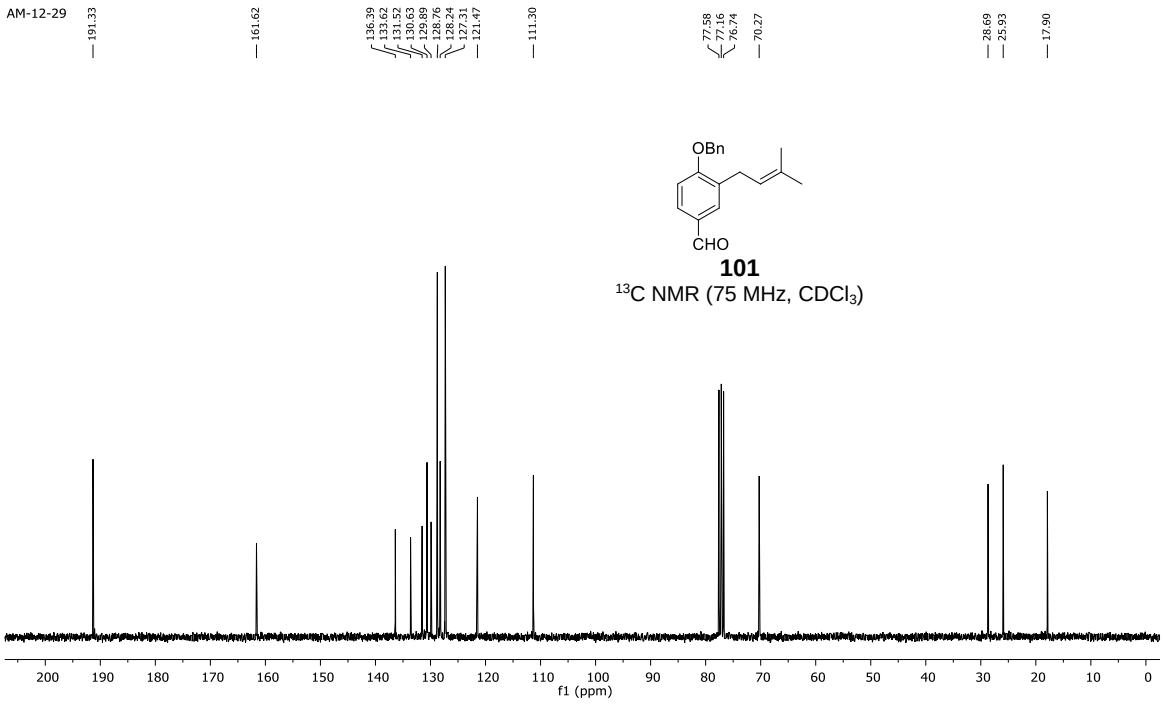
5.04
1.00
1.07
1.99
1.99
3.01
2.99
f1 (ppm)


AM-12-29
191.33
161.62
136.39
133.62
131.52
130.63
129.89
128.76
128.24
127.31
121.47
111.30
77.58
77.16
76.74
70.27
28.69
25.93
17.90
OBn
CHO
101
13C NMR (75 MHz, CDCl3)
f1 (ppm)

Chapter 5

Synthesis of (–)-(*R*,*R*)-L-factor Involving an Organocatalytic Direct Vinylogous Aldol Reaction

The work described in this chapter has been published in Synlett:

Cooze, C.; Manchoju, A.; Pansare, S. V. *Synlett*, **2017**, *28*, 2928 (invited paper).

The synthesis of (–)-(*R*,*R*)-L-factor and a portion of the catalyst survey were carried out by A. Manchoju.

5.1 Introduction

The 5-hydroxyalkyl-2(5H)furanone (*γ*-butenolide) and 5-hydroxyalkyl-2(3H)furanone (*γ*-butanolide) motif is a characteristic structural element in several natural products of polyketide origin. Prominent examples of this family are (−)-muricatacin (**1**),[1] (−)-isocladospolide B (**2**),[2] (*S*,*S*)-L-factor (**3**) and (*S*,*R*)-L-factor (**4**),[3] and (−)-botryolide E (**5**,[4] Figure 5.1) to name but only a few. In particular, muricatacin (**1**) has attracted considerable attention for its cyctotoxic activity[1] and its utility as a starting material for accessing more complex acetogenins such as (+)-squamotacin,[5] (+)-muconin,[6] (+)-*cis*-solamin A,[7] (+)-*cis*-solamin B[7] and (+)-reticulatacin.[7] The enantioselective synthesis of muricatacin has therefore been intensely investigated and several approaches to either enantiomer of muricatacin are reported.[8a-g] The synthesis of L-factors **3** and **4**, and their enantiomers which influence leukaemomycin biosynthesis in certain strains of *Streptomyces griseus*,[3] has also been actively investigated.[9]

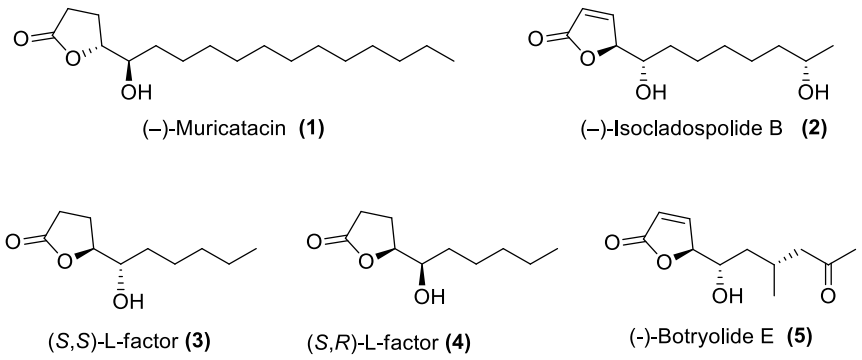
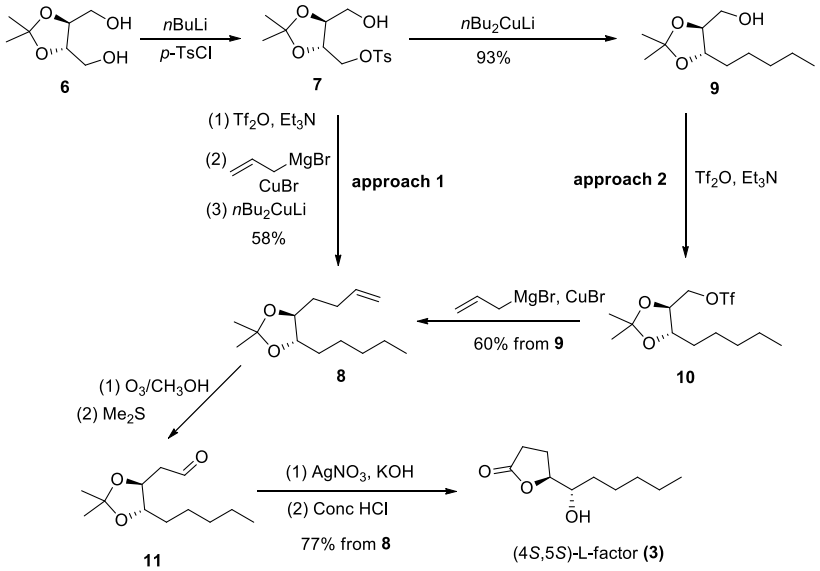


Figure 5.1 Selected *γ*-butenolide- and *γ*-butanolide-based natural products

5.2 Previous synthetic approaches to the L-factors

5.2.1 The Kotsuki synthesis of (4*S*,5*S*)-L-factor

In 1990, Kotsuki and coworkers[9c] developed an enantiospecific route to (4*S*,5*S*)-L-factor (**3**) from D-tartrate using copper(I)-catalyzed alkylation reactions (Scheme 5.1). The synthetic approach follows compound **6** derived from D-tartrate, which was treated with *p*-TsCl to give **7**, which was then converted into intermediate **8** in two ways. The first approach is a one-pot synthesis (approach 1, Scheme 5.1); the primary alcohol of **7** was treated with the triflic anhydride (Tf_2O) to give the tosyl-triflate which was allylated *in situ* with allylmagnesium bromide/CuBr. Subsequently, the addition of lithium di-*n*-butylcuprate resulted in a second alkylation by displacement of the tosyl group, to provide **8**. On the other hand (approach 2, Scheme 5.1), **7** was first alkylated with lithium di-*n*-butylcuprate to provide **9**. Activation of **9**, by conversion to the triflate **10**, followed by copper(I)-catalyzed allylation provided **8**.

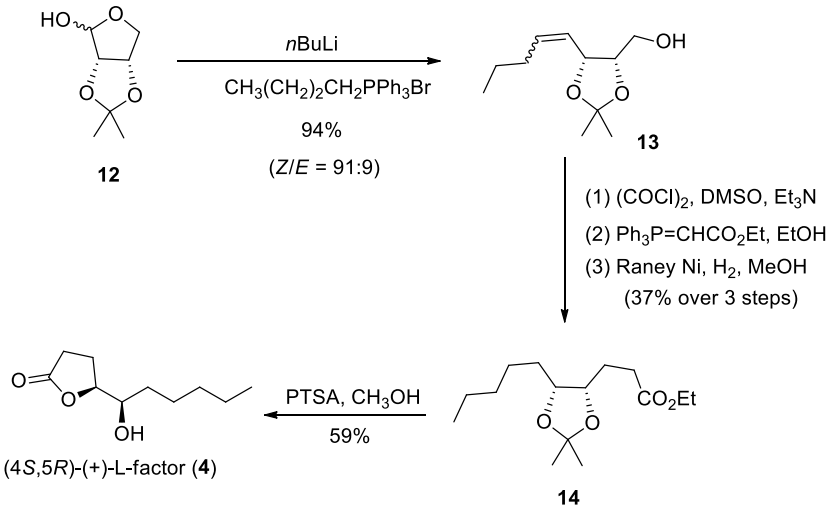


Scheme 5.1

The intermediate **8** was subjected to ozonolysis followed by dimethyl sulfide reduction to furnish the aldehyde **11** which was converted to (4*S*,5*S*)-L-factor (**3**) by Ag_2O oxidation, acetonide deprotection and *in situ* lactonization.

5.2.2 The Gallos synthesis of (+)-(4*S*,5*R*)-L-factor

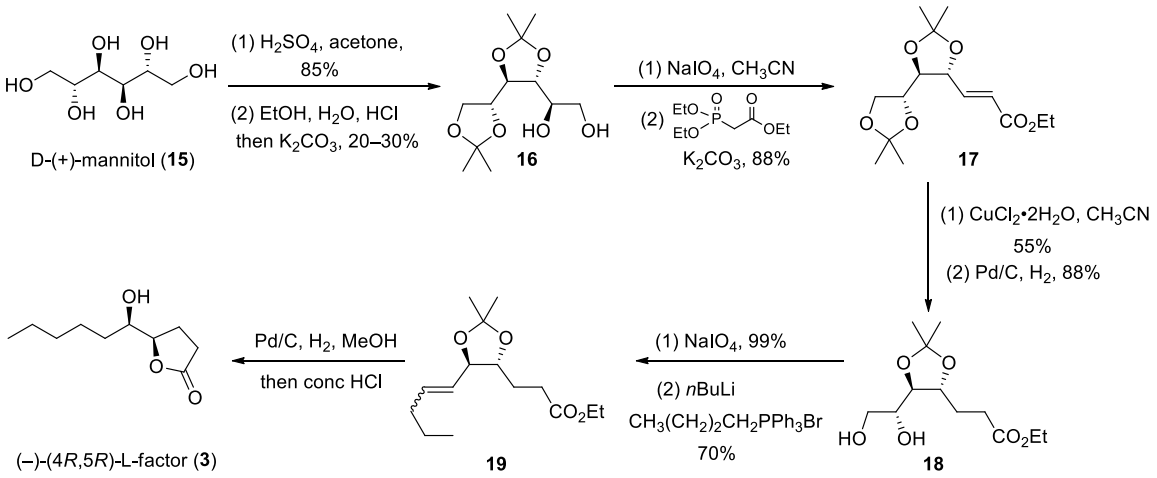
In 2009, Gallos and coworkers[9b] reported the synthesis of (+)-(4*S*,5*R*)-L-factor (**4**) from L-erythrose by employing Wittig olefination and catalytic hydrogenation as the key steps (Scheme 5.2). Lactol **12**, derived from L-erythrose, was subjected to Wittig olefination to give **13** as a mixture of *E* and *Z* alkenes. Compound **13** was transformed into the ester **14** in three steps which are, in sequence, Swern oxidation, a second Wittig olefination and catalytic reduction of the double bonds. Ester **14** was then subjected to acetonide deprotection and lactonization in the presence of PTSA to afford the enantiomerically pure natural product, (+)-(4*S*,5*R*)-L-factor (**4**) (Scheme 5.2).



Scheme 5.2

5.2.3 The Bhaumik synthesis of (–)-(4*R*,5*R*)-L-factor (ent-3)

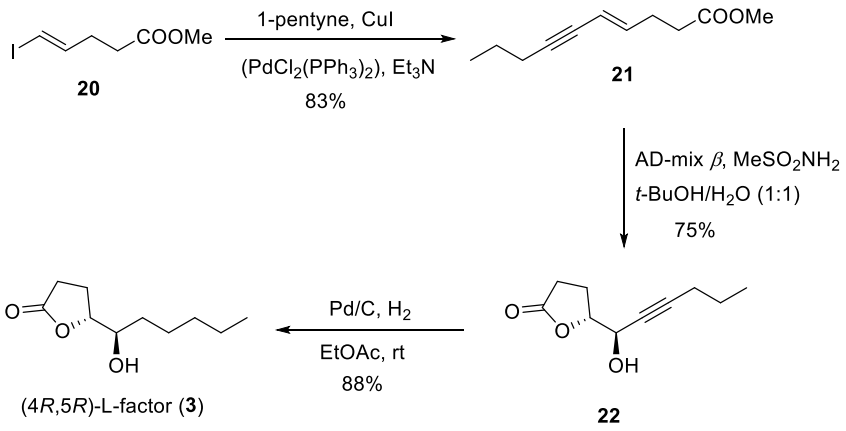
In 2014, Bhaumik and coworkers[8c] reported a chiron approach to the synthesis of (–)-(4*R*,5*R*)-L-factor (**ent-3**) from D-mannitol (**15**, Scheme 5.3). Protection of D-mannitol as the tris-acetonide **15** followed by selective hydrolysis of a terminal acetonide provided the glycol **16**. Oxidative cleavage of the vicinal diol in **16** followed by a Horner–Wadsworth–Emmons reaction of the resulting aldehyde provided the α,β-unsaturated ester **17**. Selective hydrolysis of the terminal acetonide of **17** in the presence $CuCl_2$ and subsequent hydrogenation gave the diol **18**. A periodate cleavage of **18** followed by Wittig olefination furnished alkene **19** as an *E*/Z mixture. Subsequent hydrogenation of **19** followed by acidification with concentrated HCl provided (4*R*,5*R*)-L-factor (***ent*-3**).



Scheme 5.3

5.2.4 The Raji Reddy synthesis of (4*R*,5*R*)-L-factor (*ent*-3)

In 2015, Raji Reddy and coworkers[8b] reported the asymmetric synthesis of (4*R*,5*R*)-L-factor (***ent*-3**) from iodo ester **20** involving Sonogashira cross-coupling and Sharpless asymmetric dihydroxylation as the key reactions (Scheme 5.4). Iodoalkene **20** was coupled with 1-pentyne to provide ester **21**, which was then subjected to Sharpless asymmetric dihydroxylation followed by *in situ* lactonization to give lactone **22**. Hydrogenation of **22** furnished (4*R*,5*R*)-L-factor (***ent*-3**).

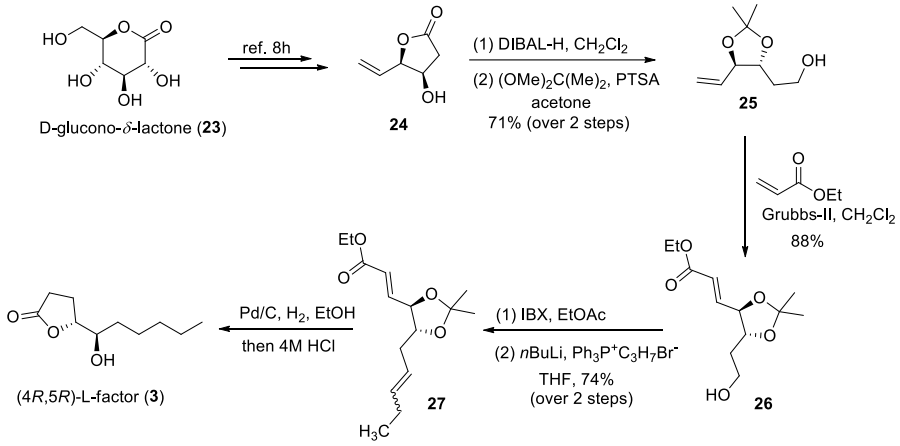


Scheme 5.4

5.2.5 The Fernandes synthesis of (4*R*,5*R*)-L-factor (*ent*-3)

In 2016, Fernandes and coworkers[8a] reported a seven-step synthesis of (4*R*,5*R*)-L-factor (***ent*-3**) from D-glucono-δ-lactone (**23**) by employing cross-metathesis and Wittig olefination reactions as the key steps (Scheme 5.5). DIBAL-H reduction of γ-vinyl-γ-lactone **24**, obtained from D-glucono-δ-lactone (**23**), followed by protection of the resulting triol as an acetonide gave **25**. Cross-metathesis of **25** with ethyl acrylate provided *E*-**26** which was converted into **27** by IBX oxidation of the alcohol and

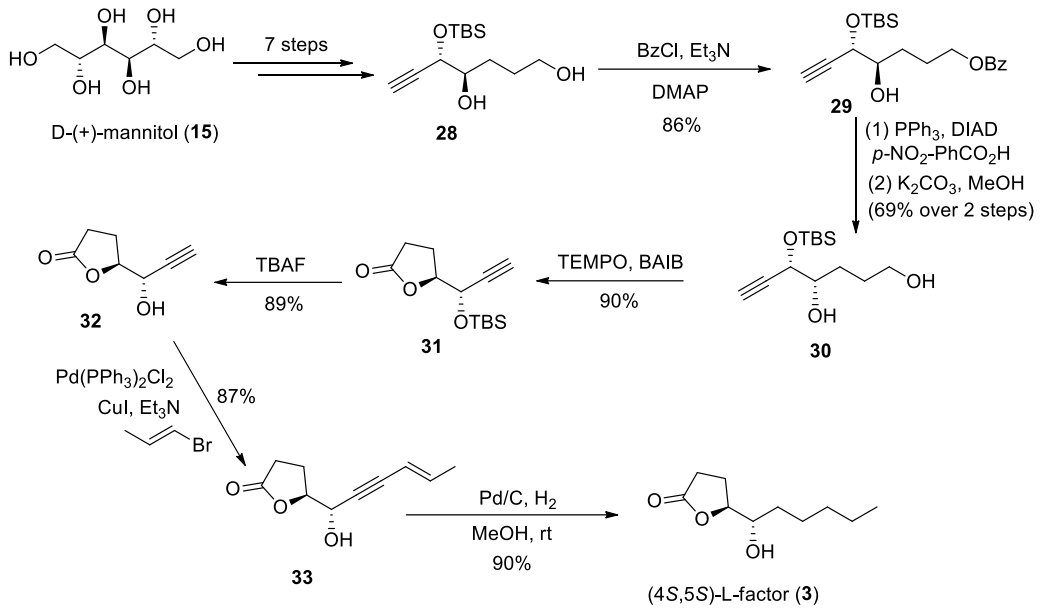
subsequent Wittig olefination. Compound **27** was then transformed into (4*R*,5*R*)-L-factor (**ent-3**) employing a one pot procedure which involves hydrogenation of double bonds in **27**, deprotection of the acetonide and *in situ* lactonization of the resulting γ-hydroxy ester.



Scheme 5.5

5.2.6 The Sabitha synthesis of (4*S*,5*S*)-L-factor (3)

In 2016, Sabitha and coworkers[9a] reported the synthesis of (4*S*,5*S*)-L-factor (**3**) from the commercially available, inexpensive starting material D-mannitol (**15**, Scheme 5.6). Diol **28** was synthesized from D-mannitol (**15**) in 7 steps. The compound **28** was converted to **30** by protection of the primary alcohol as a benzoate, Mitsunobu inversion of the secondary alcohol and ester hydrolysis. Oxidation of **30** with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) provided lactone **31**, which was further transformed into **33** by silyl ether deprotection to provide **32** followed by a Sonogashira cross-coupling of **32** with *trans*-1-bromo-1-propene. Hydrogenation of **33** furnished (4*S*,5*S*)-L-factor (**3**).



Scheme 5.6

5.3 Objective

A unifying theme for all of the known syntheses of L-factor is the stereoselective assembly of the two contiguous stereocenters, one on the lactone ring and the other in the alkyl side chain. Notably, despite the relative structural simplicity offered by L-factor, all of the reported strategies are synthetically intensive and require numerous steps (Schemes 5.1-5.6); the shortest synthesis involves five steps (Scheme 5.2)[9b] while the longest requires fourteen steps (Scheme 5.6).[9a] In addition, none of these syntheses involve stereoselective carbon-carbon bond forming reactions. Instead, they rely either on a chiral starting material[8a,c,9a-c] or an asymmetric carbon-oxygen bond formation for setting the key stereocenters in the target.[8b]

Our approach to L-factor (***ent*-3**) and other 5-hydroxyalkyl-2(5*H*)furanone derived natural products stems from our interest in the organocatalytic direct vinylogous aldol

(ODVA) reaction of γ-crotonolactones. Previous studies[10] on this reaction have established protocols that provide good stereoselectivity with aromatic aldehydes. The complementary version involving aliphatic aldehydes has been only briefly examined in these studies. In addition, in the context of L-factor syntheses, the more conventional aldol variants such as the metal-catalyzed vinylogous Mukaiyama aldol reaction of 2-trialkylsiloxyfuran[11a] and the use of crotonolactone metal enolates[11b] are also less explored. We therefore chose to examine the metal-free vinylogous aldol reaction of γ-crotonolactone with hexanal as the key step in our synthesis of and L-factor (***ent*-3**) respectively.

Retrosynthetically, the vinylogous aldol approach would potentially provide access to muricatacin (**1**) and L-factor (**3**) in only two steps from commercially available starting materials, (Figure 5.2), provided that the diastereoselectivity of the aldol reaction is in favour of the required *syn* aldol product. Even if the diastereoselectivity of the aldol reaction is moderate, conversion of the diastereomeric mixture to a diastereomerically pure *syn* aldol product via oxidation to the ketone and subsequent stereoselective reduction should be feasible.

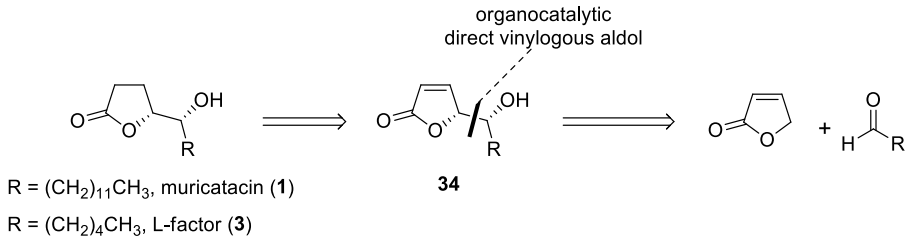
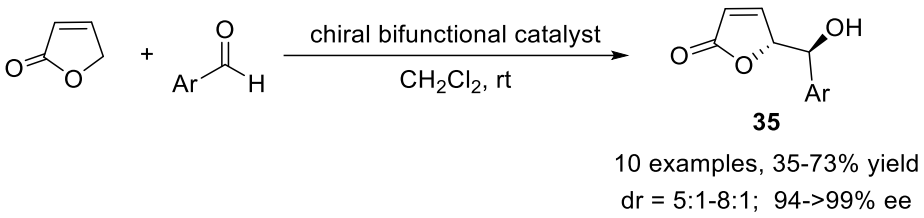


Figure 5.2 Organocatalytic direct vinylogous aldol route to 5-hydroxyalkyl butenolide and butanolide natural products.

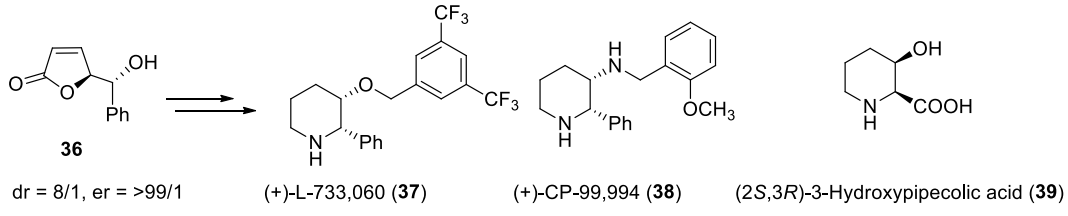
5.4 Previous work on the direct vinylogous aldol reaction of γ-crotonolactone in the Pansare group

In 2011, the Pansare group developed a methodology for the organocatalytic, asymmetric direct vinylogous aldol reaction of γ-crotonolactone with aryl aldehydes, using chiral aminothioureas and squaramides as catalysts, to access substituted γ-butenolides **35** (Scheme 5.7) with excellent enantioselectivities.[10c] The γ-butenolide derivatives are potential intermediates for the synthesis of several natural products and biologically active compounds.



Scheme 5.7

The above methodology has been used for the synthesis of substance P receptor antagonists (+)-L-733,060 (**37**)[10e] and (+)-CP-99,994 (**38**[10e], Scheme 5.8), which have been associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission. The methodology was also applied in the synthesis of 3-hydroxypipecolic acid (**39**[10e], Scheme 5.8) which is a component of tetrazomine, an antitumor antibiotic.



Scheme 5.8

5.5 Results and Discussion

We initiated our synthesis of L-factor by examining the direct vinylogous aldol reaction of γ-crotonolactone and hexanal. Previous observations[10] on a variant of this reaction employing aromatic aldehydes suggested that the use of bifunctional organocatalysts may be beneficial for the required transformation and hence selected aminosquaramides and aminothioureas were chosen as potential catalysts for the reaction (Figure 5.3).

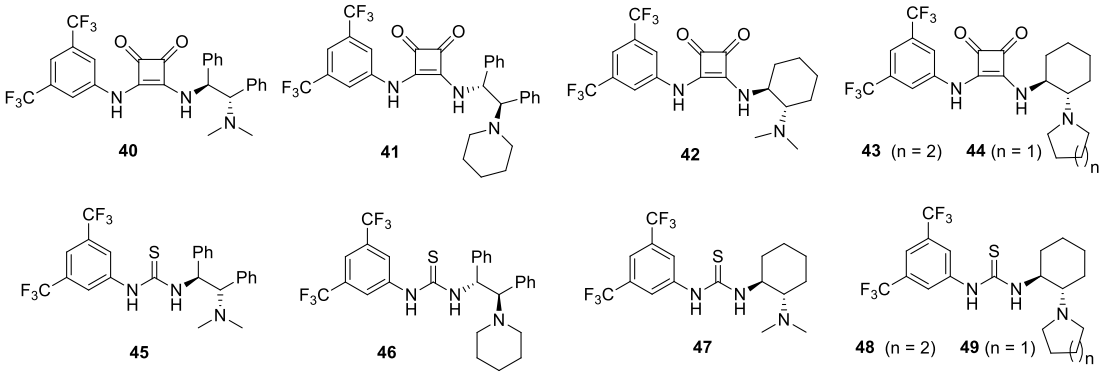


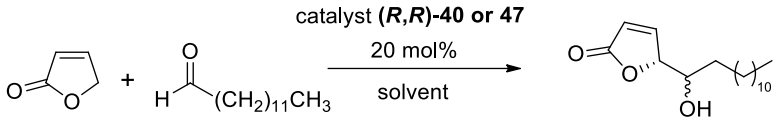
Figure 5.3 Aminosquaramide and aminothiourea catalysts selected for this study.

In simultaneous studies in the Pansare group,[12] a catalyst and solvent survey was conducted for the direct vinylogous aldol reaction between γ-crotonolactone and tridecanal, which are starting materials for the synthesis of muricatacin. The optimized conditions obtained from this study were also used for the synthesis of L-factor. Details of the solvent and catalyst survey for the reaction of γ-crotonolactone and tridecanal are described below.

In order to simplify the task of identifying the optimal reaction conditions, we first decided to identify a suitable solvent for the vinylogous aldol reaction by conducting the

reaction with (*R*, *R*)-aminosquaramide **40** and aminothiourea **47**, both of which have a dimethylamino functionality, in a selection of solvents. These studies indicated that while dichloromethane was the solvent of choice for **40** (*anti*/*syn* = 3.3:1, 98% ee for *anti* **50**, and 77% ee for *syn* **50**, Table 5.1, entry 2), the optimal solvent for **47** (*anti*/*syn* = 1.5:1, 57% ee for anti **50**, and 64% ee for syn **50**, Table 5.1, entry 9) was THF in terms of diastereoselectivity and enantioselectivity (a complete solvent survey was examined by C. Cooze in the Pansare group[12]).

Table 5.1: Solvent survey for organocatalytic direct vinylogous aldol reaction of γ-crotonolactone and tridecanal



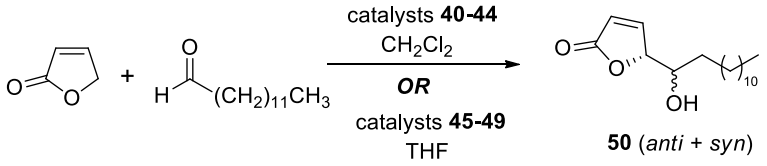
50 (*anti* + *syn*)

Entry[a]	Cat.	Solvent	Yield (%)	dr[b] (*anti*:*syn*)	ee (%) *anti*/*syn*
1	**(*R*,*R*)-40**	EtOAc	5	3.0:1	97/86
2		CH_2Cl_2	21	3.3:1	98/77
3		THF	4	2.7:1	44/85
4		toluene	6	3.2:1	96/60
5		DMF	< 2	-	66/81
6		diethyl ether	6	3.9:1	90/71
7	**47**	EtOAc	30	1.3:1	57/61
8		CH_2Cl_2	38	1.2:1	34/28
9		THF	38	1.5:1	57/64
10		toluene	35	1.3:1	33/26
11		DMF	16	1.2:1	64/74
12		diethyl ether	37	1:1	15/3

[a]2 equiv. of crotonolactone. [b]^{1}H NMR of isolated products

With this information in hand, a study of the effect of catalyst structure on the aldol reaction in the optimal solvent (dichloromethane for the aminosquaramides **40**–**44** and THF for the aminothioureas **45–49**) was undertaken. These results are summarized in Table 5.1.

Table 5.2 Organocatalytic direct vinylogous aldol reaction of γ-crotonolactone and tridecanal



Entry	Cat.[a]	Time (days)	50 (%)	dr (*anti*/*syn*)	ee (%) *anti*/*syn*
1	**40**	15	32	3.3/1	98/77
2	**41**	13	8	3.4/1	41/61
3[b]	**42**	12	29	2.1/1	81/73
4	**43**	12	65	2.2/1	81/54
5[b]	**44**	12	28	1.1/1	75/51
6	**45**	13	25	2.4/1	99/26
7[b]	**46**	11	6	1.6/1	84/80
8	**47**	10	38	1.5/1	64/74
9	**48**	13	22	2.0/1	81/69
10[b]	**49**	11	3	1.3/1	78/58

[a]dichloromethane as the solvent for catalysts **40–44**, and THF for catalysts **45–49**.

[b]were carried out by Manchoju A.

All of the selected catalyst candidates were capable of facilitating the vinylogous aldol reaction. Although the diastereoselectivity of the reaction was moderate (highest dr = 3.4:1, *anti*/*syn*), it may be noted that this reaction offers the shortest assembly of the 5-hydroalkyl γ-butenolide motif. On the basis of our previous studies with aromatic

aldehydes,[10c] the absolute configuration at the lactone stereocenter in both diastereomers of **50** is assigned as *R*. Since our strategy for conversion of the mixture of diastereomers of **50** to the required *syn* diastereomer relied on an oxidation/reduction protocol, it was important that the *syn* diastereomer obtained from the aldol reaction is also of high enantiomeric excess. Hence, although catalysts **40** and **45** both provided the *anti* diastereomer of **50** with high ee, catalyst **40** was chosen for further studies since it not only offered slightly higher diastereoselectivity than **45**, but also provided *syn* **50** with much higher ee compared to catalyst **45** (Table 5.2, entries 1 and 6).[13]

5.5.1 Stereochemical model for the vinylogous aldol reaction of γ-crotonolactone with aliphatic aldehydes

A plausible transition state has been proposed for the vinylogous aldol reaction of γ-crotonolactone with aliphatic aldehydes (Figure 5.4). The carbonyl group of the electrophile (aldehyde) is hydrogen bonded with the squaramide functionality and the deprotonated nucleophile is associated with the ammonium group in the catalyst by ionic interaction. Previous studies[14] on the triethylamine-catalyzed reaction of γ-crotonolactone with aldehydes (used for the preparation of racemic products) has an intrinsic preference for the *anti* diastereomer (dr = ~2/1). The present results suggest that the hydrogen bonding functionality in the catalyst enhances this diastereoselectivity.

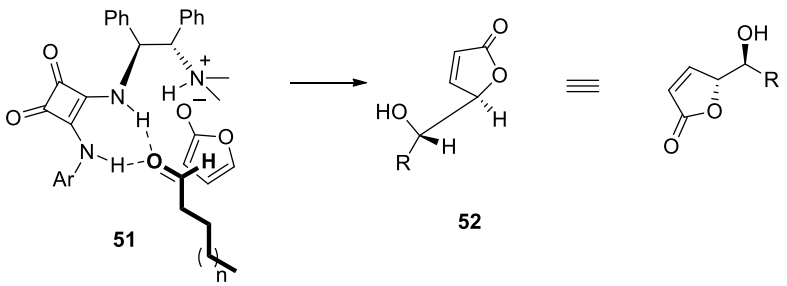
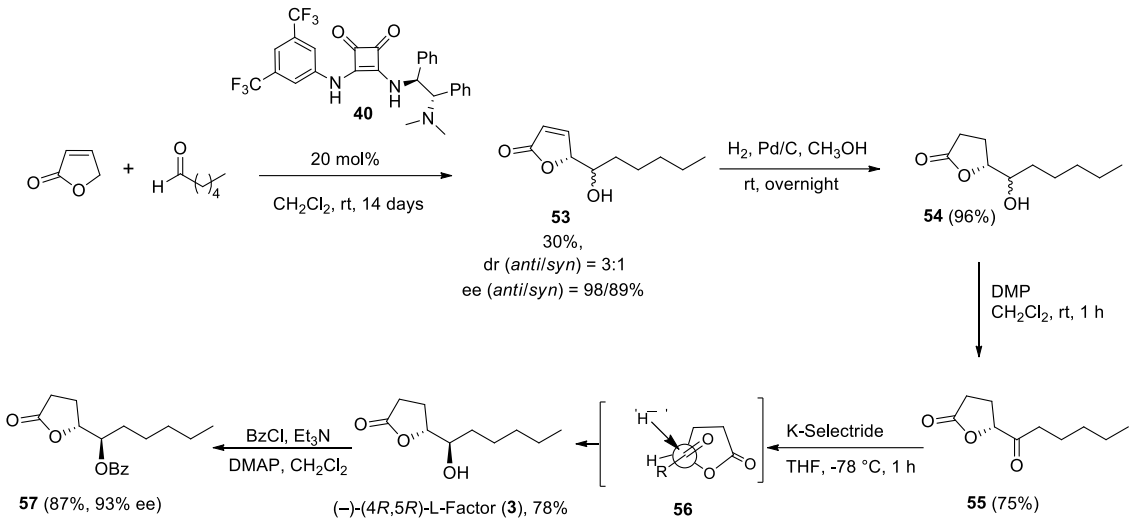


Figure 5.4 Proposed transition state for the ODVA reaction leading to the *anti* aldol product.

Having established the conditions for the key aldol reaction, we proceeded to complete the synthesis of (–)-L-factor. As with tridecanal, the aldol reaction of γ-crotonolactone with hexanal in the presence of catalyst **40**, gave the required aldol product **53** (Scheme 5.9, 30%, *anti*/*syn* = 3:1) with good enantiomeric excess for both diasteromers (98% ee for *anti* **53**, and 89% ee for *syn* **53**). Subsequent hydrogenation of **53** gave **54** (96%, Scheme 5.9). Conversion of **54** to (–)-L-factor (**3**) was achieved in two steps. Oxidation of **54** with DMP provided the ketone **55** (75%, Scheme 5.9). Diastereoselective reduction[15] of **55** with K-Selectride®, presumably *via* the Felkin-Anh mode (**56**),[16] gave (–)-L-factor (**3**). Chiral HPLC analysis of **3** was difficult due to the absence of chromophore. Hence, the enantiomeric excess of **3** was determined by HPLC analysis of the derived benzoate ester **57** (87%, 93% ee, Scheme 5.9).



Scheme 5.9 Synthesis of (–)-L-factor (***ent*-3**).

5.6 Conclusion

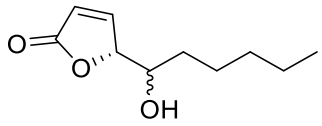
In conclusion, the shortest reported synthesis of (–)-(*R*,*R*)-L-factor (***ent*-3**) was developed using an organocatalytic direct vinylogous aldol reaction as the key step. These studies provide a point of reference for future studies on the organocatalytic direct vinylogous aldol reaction of γ-crotonolactone and unbranched aliphatic aldehydes.

5.7 Experimental section

General:

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system.

(5*R*)-5-(1-Hydroxyhexyl)furan-2(5*H*)-one (53):

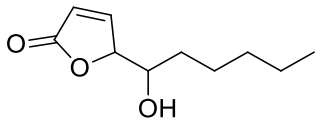


To a solution of 2(5*H*)-furanone (0.69 mL, 9.7 mmol) and the hexanal (0.59 mL, 4.8 mmol) in dichloromethane (7mL) was added the (*S,S*)-aminosquaramide catalyst **40** (533 mg, 0.966 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 days and the solvent was removed under reduced pressure. The crude product was purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1), 266 mg (30%) of **53** as a colorless liquid (*anti*:*syn* = 3:1).

R_f = 0.20 (CH_2Cl_2/EtOAc, 4:1); IR (neat): 3428 (br), 2954, 2929, 2859, 1740, 1163, 1101, 1028, 819 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): ***Anti* diastereomer (major)**: δ 7.54 (dd,

1H, *J* = 5.7, 1.5 Hz, COCH=C*H*), 6.19 (ddd, 1H, *J* = 5.7, 2.0, 0.1 Hz, COC*H*=CH), 4.96 (dt, 1H, *J* = 4.7, 1.7 Hz, CH=CHC*H*), 3.92-3.82 (m, 1H, C*H*OH), 2.11 (d, 1H, *J* = 5.4 Hz, O*H* (D_2O exchange)), 1.68-1.22 (m, 8H, CH_2), 0.90 (t, 3H, *J* = 6.5 Hz, CH_3); **Visible resonances of *syn* diastereomer (minor)**: δ 7.46 (dd, 1H, *J* = 5.7, 1.5 Hz, COCH=C*H*), 4.99 (dd, 1H, *J* = 3.2, 1.4 Hz, CH=CHC*H*), 3.80-3.71 (m, 1H, C*H*OH), 1.68-1.22 (m, 8H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): ***Anti* diastereomer (major):** δ 173.1 (*C*(O)O), 153.6 (COCH=*C*H), 122.8 (CO*C*H=CH), 86.16 (CH=CH*C*H), 71.5 (C*H*OH), 33.1 (*C*H_2), 31.6 (*C*H_2), 25.22 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3); **Visible resonances of *syn* diastereomer (minor):** δ 173.0 (*C*(O)O), 153.9 (COCH=*C*H), 122.7 (CO*C*H=CH), 86.21 (CH=CH*C*H), 71.8 (C*H*OH), 33.2 (*C*H_2), 25.16 (*C*H_2); HRMS (APPI, pos): 184.1091 (184.1099 calc for $C_{10}H_{16}O_3$ $(M)^+$) and 185.1162 (185.1178 calc for $C_{10}H_{17}O_3$ $(M+H)^+$); Chiralpak AS-H (hexanes/2-propanol 95:5, flow rate 1 mL min^{-1}, 254 nm): t_1 = 20.18 min (major *anti*), t_2 = 27.63 min, (major *syn*), t_3 = 42.80 min (minor *syn*), t_4 = 55.46 min (minor *anti*). ee: 98% (anti); ee: 89% (*syn*).

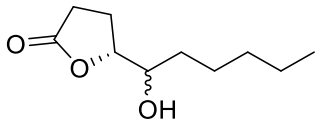
***rac* 5-(1-Hydroxyhexyl)furan-2(5*H*)-one (53):**



To a solution of hexanal (0.34 mL, 2.8 mmol) and 2-(triisopropylsilyloxy)furan (800 mg, 3.32 mmol) in THF (6 mL) was added $Cu(OTf)_2$ (100 mg, 0.277 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 48 h. The mixture was then

concentrated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) 188 mg (36%) of racemic **53** (dr = 1.7:1) as a colorless liquid.

(5*R*)-5-(1-Hydroxyhexyl)dihydrofuran-2(3*H*)-one (54):

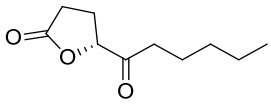


To a solution of the hydroxy γ-butenolide **53** (170 mg, 0.920 mmol) in methanol (5 mL) was added Pd/C (10%, 98 mg) and the mixture was stirred at room temperature under an atmosphere of hydrogen (balloon) overnight. After completion of the reaction (NMR of an aliquot) the mixture was filtered through a pad of Celite and the residue washed with methanol (2 × 20 mL). The combined filtrates were concentrated under reduced pressure to provide the product 165 mg (96%) of **54** as a colorless liquid (*anti*:*syn* = 3:1). The crude product was used in the next step without purification.

R_f= 0.22 (CH_2Cl_2/EtOAc, 4:1); IR (neat): 3434 (br), 2954, 2930, 2859, 1759, 1460, 1185, 1073 1054, 1024, 992, 927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): ***Anti* diasteromer (major):** δ 4.44 (td, 1H, *J* = 7.3, 3.2 Hz, OC*H*), 3.97-3.90 (m, 1H, C*H*OH), 2.69-2.44 (m, 2H, CH_2), 2.35-2.05 (m, 2H, CH_2), 2.05 (br s, 1H, O*H*), 1.60-1.21 (m, 8H, 4 × CH_2), 0.90 (t, 3H, *J* = 6.7 Hz, CH_3); **Visible resonances of *syn* diastereomer (minor):** δ 3.62-3.53 (m, 1H, C*H*OH), 2.69-2.44 (m, 2H, CH_2), 2.32-2.05 (m, 2H, CH_2), 1.60-1.21 (m, 8H, 2 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) ***Anti* diasteromer (major):** δ 177.5 (*C*(O)O), 82.8 (O*C*H), 71.4 (*C*HOH), 31.9 (*C*H_2), 31.7 (*C*H_2), 28.7 (*C*H_2), 25.3 (*C*H_2), 22.5 (*C*H_2), 21.1 (*C*H_2), 14.0 (*C*H_3); **Visible resonances of *syn* diastereomer (minor):** 177.2 (*C*(O)O),

83.0 (O*C*H), 73.7 (*C*HOH), 32.9 (*C*H_2), 31.7 (*C*H_2), 25.1 (*C*H_2), 24.1 (*C*H_2); HRMS (APPI, pos): 186.1250 (186.1256 calc for $C_{10}H_{18}O_3$ $(M)^+$) and 187.1323 (187.1334 calc for $C_{10}H_{19}O_3$ $(M+H)^+$).

(*R*)-5-Hexanoyldihydrofuran-2(3*H*)-one (55):



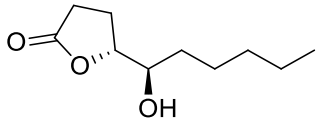
To a solution of the hydroxy γ-butanolide **54** (144 mg, 0.770 mmol) in dichloromethane (5 mL) was added Dess-Martin periodinane (657 mg, 1.54 mmol) at room temperature and the mixture was stirred for 1 h. Saturated $NaHCO_3$ (5 mL) was added, the mixture was stirred for 5 min and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 97:3), 107 mg (75%) of **55** as a colorless liquid.

R_f = 0.34 (CH_2Cl_2/EtOAc, 9:1); $[\alpha]_D^{23}$ = –11.6 (c = 1.80, MeOH); IR (neat): 2956, 2932, 2871, 1782, 1721, 1161, 1135, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.87-4.80 (m, 1H, OC*H*), 2.70-2.43 (m, 5H, C*H*$_2$), 2.32-2.17 (m, 1H, C*H*$_2$), 1.61 (quint, 2H, *J* = 7.3 Hz, C*H*$_2$), 1.40-1.22 (m, 4H, C*H*$_2$), 0.90 (t, 3H, *J* = 6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7 (*C*=O), 176.1 (*C*(O)O), 81.8 (O*C*H), 38.8 (*C*H_2), 31.2 (*C*H_2), 27.4 (*C*H_2), 24.6 (*C*H_2), 22.6 (*C*H_2), 22.4 (*C*H_2), 13.9 (*C*H_3); HRMS (APPI, pos): 184.1095 (184.1099 calc for $C_{10}H_{16}O_3$ $(M)^+$) and 185.1166 (185.1178 calc for $C_{10}H_{17}O_3$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexanes/*i*-PrOH, 95:5, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 13.12 min; t_{minor} = 15.20 min; 97% ee.

***rac* 5-Hexanoyldihydrofuran-2(3*H*)-one (55):**

DMP oxidation of *rac*-**54** provided racemic ketone **55**.

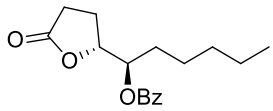
(*R*)-5-((*R*)-1-Hydroxyhexyl)dihydrofuran-2(3*H*)-one ((–)-L-factor (*ent*-3)):



To a solution of the ketone **55** (60 mg, 0.33 mmol) in dry THF (2 mL) was added K-Selectride (0.48 mL, 0.49 mmol, 1.0 M in THF) at –78 °C and the mixture was stirred for 1 h. Saturated NH_4Cl (5 mL) was added at –78 °C and the mixture was warmed to room temperature. The mixture was then extracted with ethyl acetate (3 × 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1), 48 mg (78%) of ***ent*-3** as a white solid.

R_f = 0.22 (CH_2Cl_2/EtOAc, 4:1); $[\alpha]_D^{23}$ = –29.3 (c = 1.27, $CHCl_3$); mp: 41-43 °C; lit.[8a] $[\alpha]_D^{25}$ = –27.1 (c = 0.6, $CHCl_3$), mp: 42-44 °C; lit.[8b] $[\alpha]_D^{23}$ = –32.8 (c = 1.54, $CHCl_3$), mp: 45-48 °C; IR: 3450 (br), 2954, 2928, 2858, 1765, 1185, 1133, 1075, 1057, 1023, 992, 929, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (td, 1H, *J* = 7.3, 4.4 Hz, OC*H*), 3.62-3.52 (br m 1H, C*H*OH), 2.69-2.46 (m, 2H, CH_2), 2.32-2.01 (m, 3H, CH_2, O*H* (D_2O exchange)), 1.62-1.21 (m, 8H, CH_2), 0.89 (t, 3H, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3 (*C*(O)O), 83.0 (O*C*H), 73.6 (*C*HOH), 32.9 (*C*H_2), 31.7 (*C*H_2), 28.7 (*C*H_2), 25.1 (*C*H_2), 24.1 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3); HRMS (APPI, pos): 186.1252 (186.1256 calc for $C_{10}H_{18}O_3$ $(M)^+$) and 187.1325 (187.1334 calc for $C_{10}H_{19}O_3$ $(M+H)^+$).

(*R*)-1-((*R*)-5-Oxotetrahydrofuran-2-yl)hexyl benzoate (57):



To a solution of L-factor (***ent*-3**) (20 mg, 0.11 mmol) in dichloromethane (1 mL) were added triethylamine (30 µL, 0.22 mmol) and DMAP (4.0 mg, 3.2×10^{-2} mmol) followed by BzCl (25 µL, 0.22 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 15 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (CH_2Cl_2), 27 mg (87%) of **57** as a pale-yellow liquid.

R_f = 0.29 (CH_2Cl_2); IR: 2955, 2929, 2860, 1776, 1716, 1452, 1266, 1175, 1108, 1068, 1025, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H, Ar*H*), 7.63-7.55 (m, 1H, Ar*H*), 7.51-7.42 (m, 2H, Ar*H*), 5.28 (ddd, 1H, *J* = 8.1, 5.3, 2.6 Hz, BzOC*H*), 4.74 (ddd, 1H, *J* = 8.1, 5.3, 2.6 Hz, OC*H*), 2.53-2.45 (m, 2H, CH_2), 2.44-2.27 (m, 1H, CH_2), 2.12-1.98 (m, 1H, CH_2), 1.94-1.72 (m, 2H, CH_2), 1.46-1.20 (m, 6H, CH_2), 0.87 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9 (*C*(O)O), 166.0 (*C*(O)O), 133.4 (Ar*C*), 129.8 (2 × Ar*C*), 129.5 (ArC_{ipso}), 128.6 (2 × Ar*C*), 80.0 (O*C*H), 75.0 (BzO*C*H), 31.5 (*C*H_2), 30.8 (*C*H_2), 28.1 (*C*H_2), 24.9 (*C*H_2), 24.0 (*C*H_2), 22.4 (*C*H_2), 13.9 (*C*H_3); HRMS (APPI, pos): 290.1517 (290.1518 calc for $C_{17}H_{22}O_4$ $(M)^+$) and 291.1590 (291.1596 calc for $C_{17}H_{23}O_4$ $(M+H)^+$); HPLC: Chiralcel OD-H (hexanes/*i*-PrOH, 97:3, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 10.49 min; t_{major} = 12.21 min; 93% ee.

5.8 References

1. Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137.

2. (a) Smith, C. J.; Abbanat, D.; Bernon, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Tahir, A.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142. (b) Gesner, S.; Cohen, N.; Ilan, M.; Yarden, O.; Carmeli, S. *J. Nat. Prod.* **2005**, *68*, 1350.

3 Grafe, U.; Reinhardt, G.; Schade, W.; Krebs, D.; Eritt, I.; Fleck, W. F.; Heinrich, E.; Radics, L. *J. Antibiot.* **1982**, 609.

4. Sy, A. A.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2008**, *71*, 415.

5. Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067.

6. Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993.

7. Konno, H.; Makabe, H.; Hattori, Y.; Nosaka, K.; Akaji, K. *Tetrahedron* **2010**, *66*, 7946.

8 (a) Chaudhari, D. A.; Ingle, A. B.; Fernandes, R. A. *Tetrahedron: Asymmetry* **2016**, *27*, 114. (b) Raji Reddy, C.; Suman, D.; Narsimha Rao, N. *Helv. Chim. Acta* **2015**, *98*, 967. (c) Chatterjee, S.; Manna, A.; Bhaumik, T. *Tetrahedron: Asymmetry* **2014**, *25*, 1624. (d) Doran, R.; Guiry, P. J. *Synthesis* **2014**, *46*, 761. (e) Dong, H.-B.; Yang, M.-Y.; Liu, B.; Wang, M.-A. *J. Asian Nat. Prod. Res.* **2014**, *16*, 847. (f) Gonzalez, M.; Gandara, Z.; Martinez, A.; Gomez, G.; Fall, Y. *Synthesis* **2013**, *45*, 1693. (g) Gonzalez, M.; Gandara, Z.; Pazos, G.; Gomez, G.; Fall, Y. *Synthesis* **2013**, *45*, 625. (h) Fernandes, R. A.; Kattanguru, P. *Asian J. Org. Chem.* **2013**, *2*, 74.

9. Selected syntheses: (a) Nagi Reddy, K.S.; Sabitha,G.; Poornachandra, Y.; Kumar, G. C. *RSC Adv.,* **2016**, *6*, 101501. (b) Totokotsopoulos, S. M.; Anagnostaki, E.E.; Stathakis, C.-I.; Yioti, E. G.; Hadjimichael, C. Z.; Gallos, J. K. *ARKIVOC* **2009**, *x*, 209. (c) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417. (d) Fujisawa, T.; Kojima, E.; Ito, T. Sato, T. *Chem. Lett.* **1985**, 1751. (e) Larchevêque, M.; Lalande, J. *J. Chem. Soc. Chem. Commun.* **1985**, 83.

10. Organocatalytic vinylogous aldol reactions of unsubstituted γ-crotonolactone: (a) Sakai, T.; Hirashima, S.; Yamashita, Y.; Arai, R.; Nakashima, K.; Yoshida, A.; Koseki, Y.; Miura, T. *J. Org. Chem.* **2017**, *82*, 4661. (b) Claraz, A.; Oudeyer, S.; Levacher, V. *Adv. Synth. Catal.* **2013**, *355*, 841. (c) Pansare, S. V.; Paul, E. K. *Chem. Commun.* **2011**, *47*, 1027. (d) Yang, Y.; Zheng, K.; Zhao, J.; Shi, J.; Lin, L..; Liu, X.; Feng, X. *J. Org. Chem.* **2010**, *75*, 5382. (e) Pansare. S.V; Paul. E. K, *Org. Biomol. Chem*. **2012**, *10*, 2119.

11. (a) Szlosek, M.; Franck, X.; Figadère, B.; Cave, A. *J. Org. Chem.* **1998**, *63*, 5169. (b) Bella, M.; Piancatelli, G.; Squarcia, A. *Tetahedron* **2001**, *57*, 4429

12. Christopher Cooze in the Pansare group. Cooze, C. undergraduate thesis, Memorial University, **2016**.

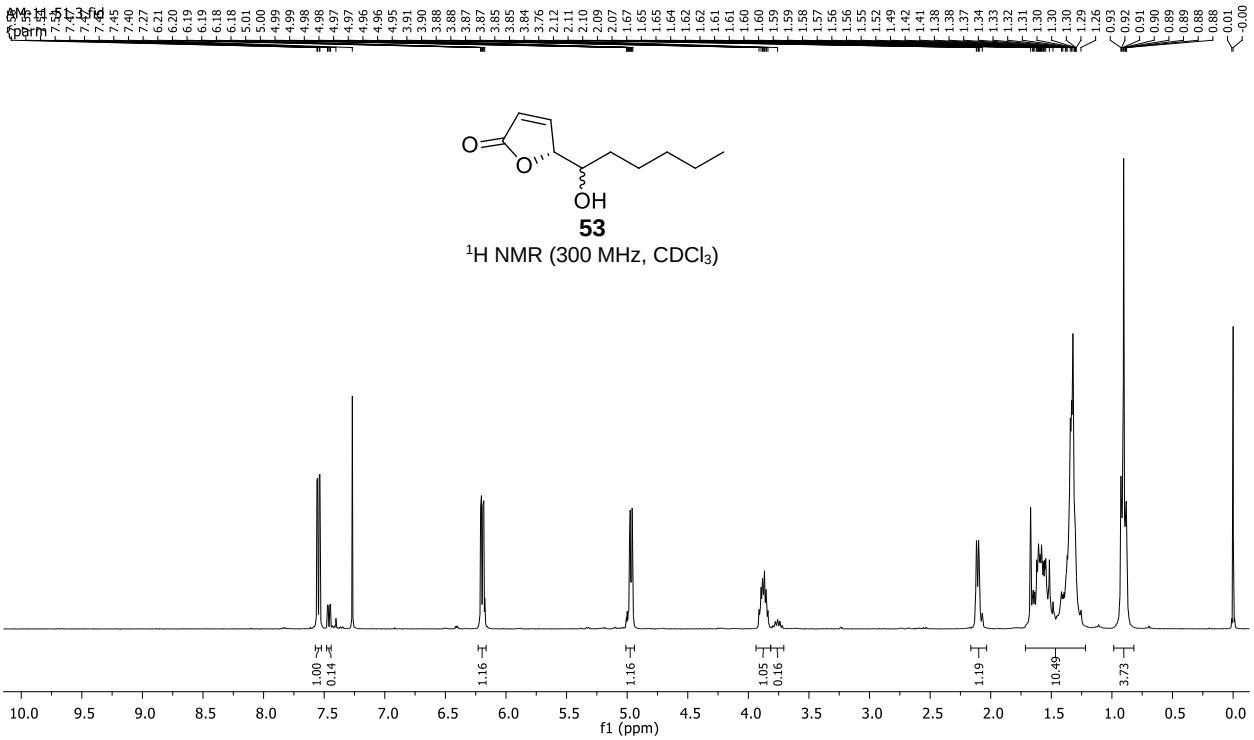
13 The *syn* and *anti* diastereomers in **53** were assigned by comparison of the trend in chemical shift of their methine hydrogens with that in structurally related aldol products obtained from aromatic aldehydes (ref. 10c). These assignments were subsequently confirmed by the conversion of *syn* **53** to **3**.

14. Eldho K. Paul in the Pansare group. Paul, E. K. Ph.D. Dissertation, Memorial University, **2013**.

15 Cavé, A.; Chaboche, C.; Figadère, B.; Harmange, J. C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Lafitte, J.; Quéro, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 617

16. Anh, N. Y. *Top. Curr. Chem.*, **1980**, *88*, 145.

5.9 Selected ^{1}H NMR and ^{13}C NMR Spectra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(ppm)
O
O
OH
53
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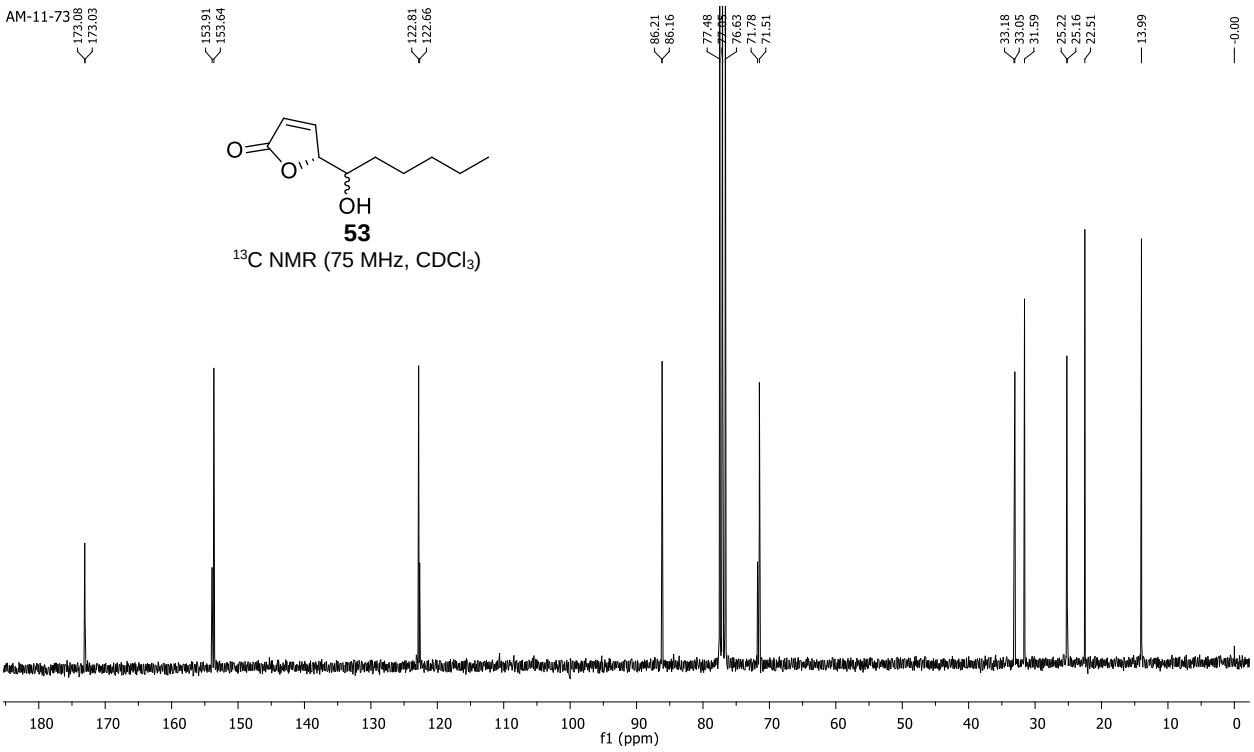
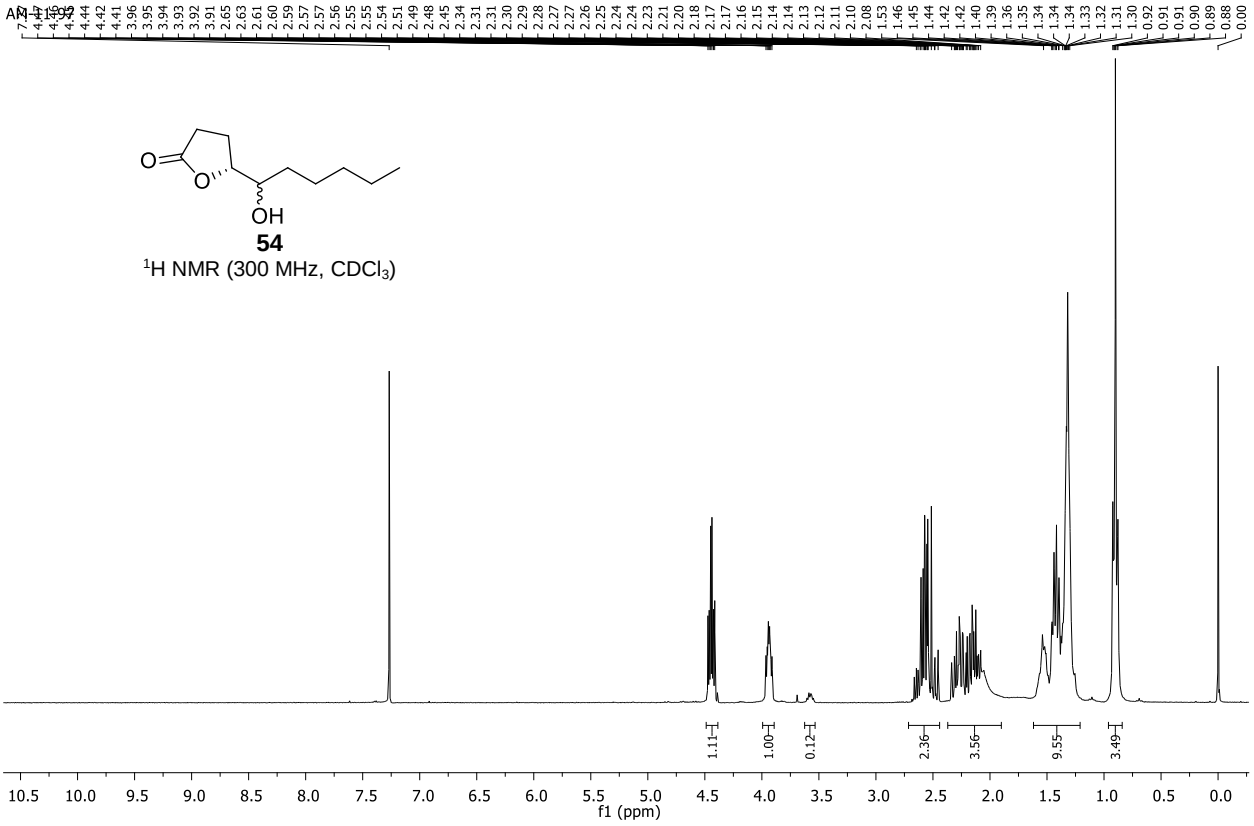
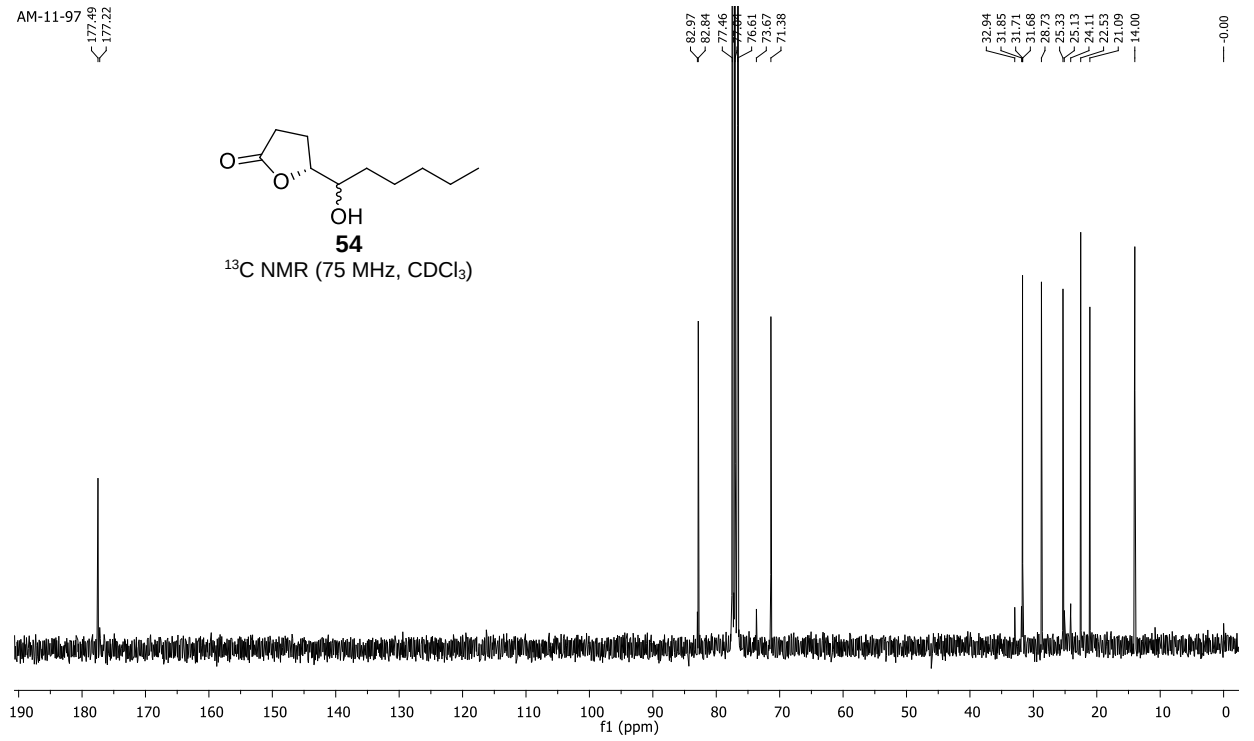
0.14
1.16
1.16
1.05
0.16
1.19
10.49
3.73
f1 (ppm)


AM-11-73
173.08
173.03
153.91
153.64
122.81
122.66
86.21
86.16
77.48
76.63
71.78
71.51
33.18
33.05
31.59
25.22
25.16
22.51
13.99
-0.00
O
O
OH
53
13C NMR (75 MHz, CDCl3)
f1 (ppm)



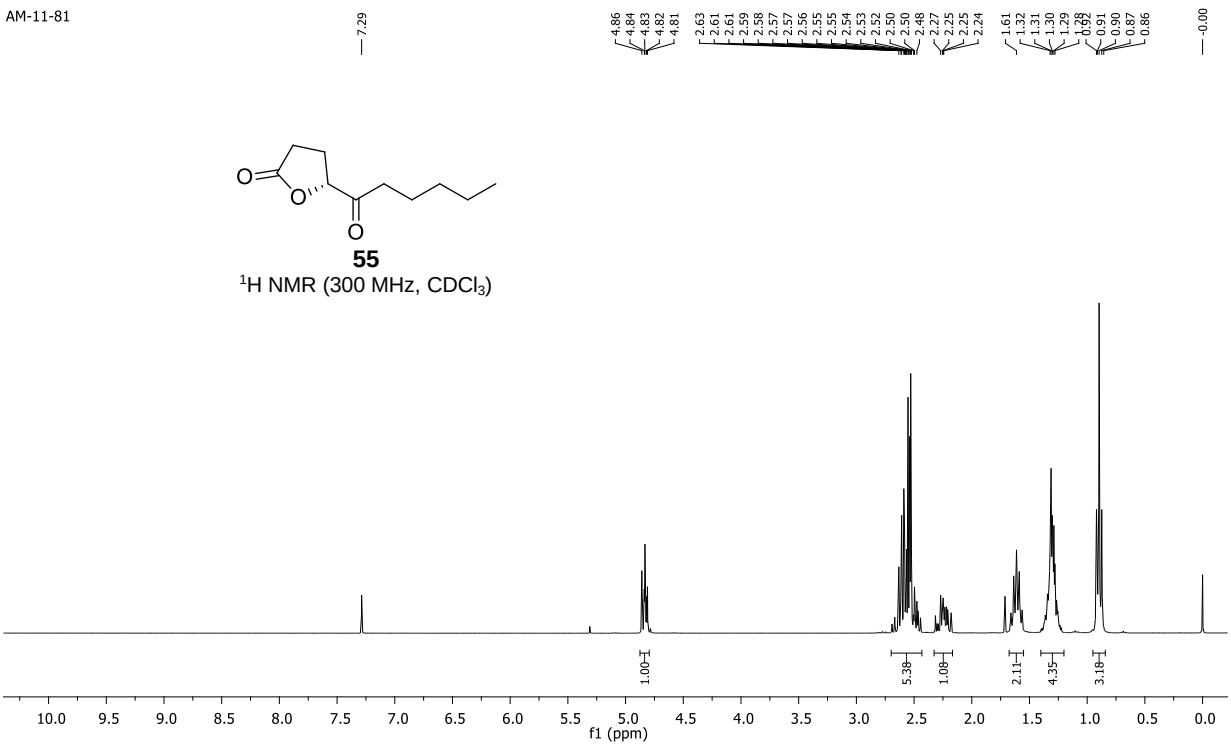
54

^{1}H NMR (300 MHz, $CDCl_3$)



54

^{13}C NMR (75 MHz, $CDCl_3$)


AM-11-81
7.29
4.86
4.84
4.83
4.82
4.81
2.63
2.61
2.61
2.59
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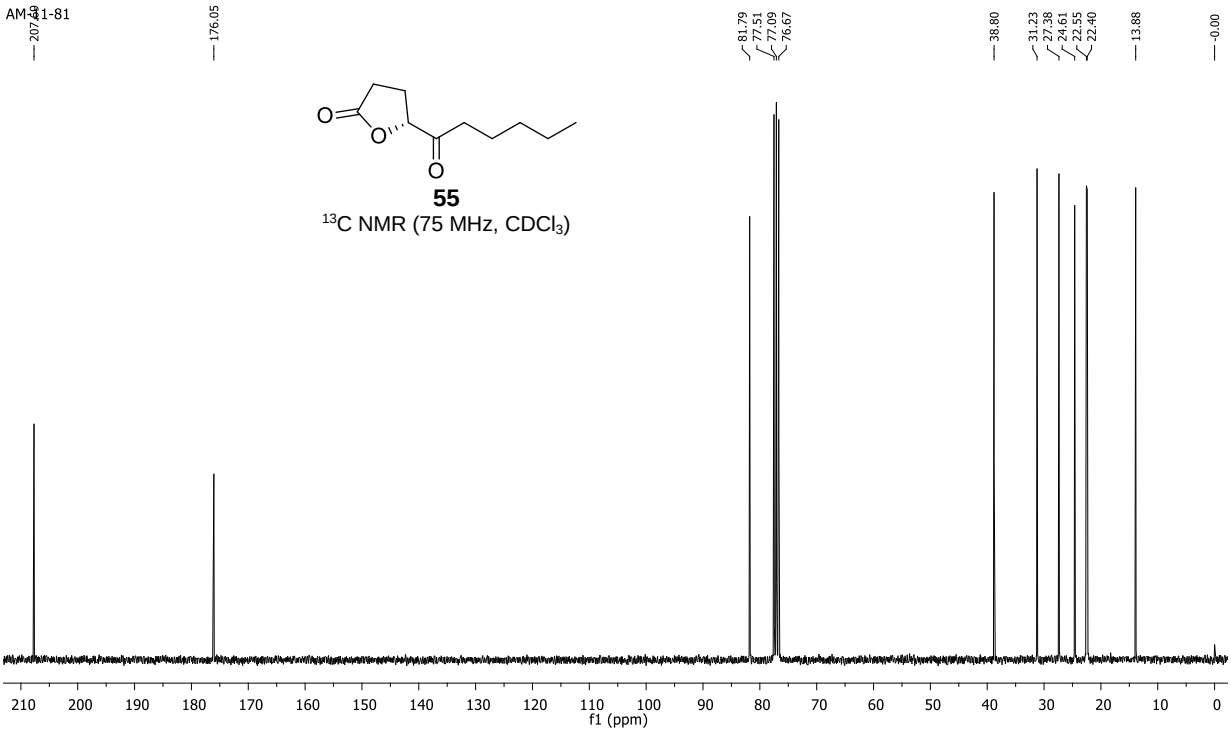
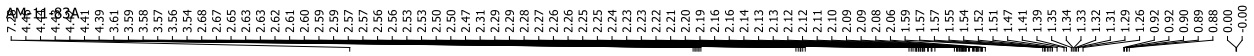
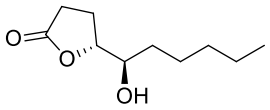
2.57
2.57
2.56
2.55
2.55
2.54
2.53
2.52
2.50
2.50
2.48
2.27
2.25
2.25
2.24
1.61
1.32
1.31
1.30
1.29
0.92
0.91
0.90
0.87
0.86
-0.00
O
O
O
55
1H NMR (300 MHz, CDCl3)
1.00
5.38
1.08
2.11
4.35
3.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

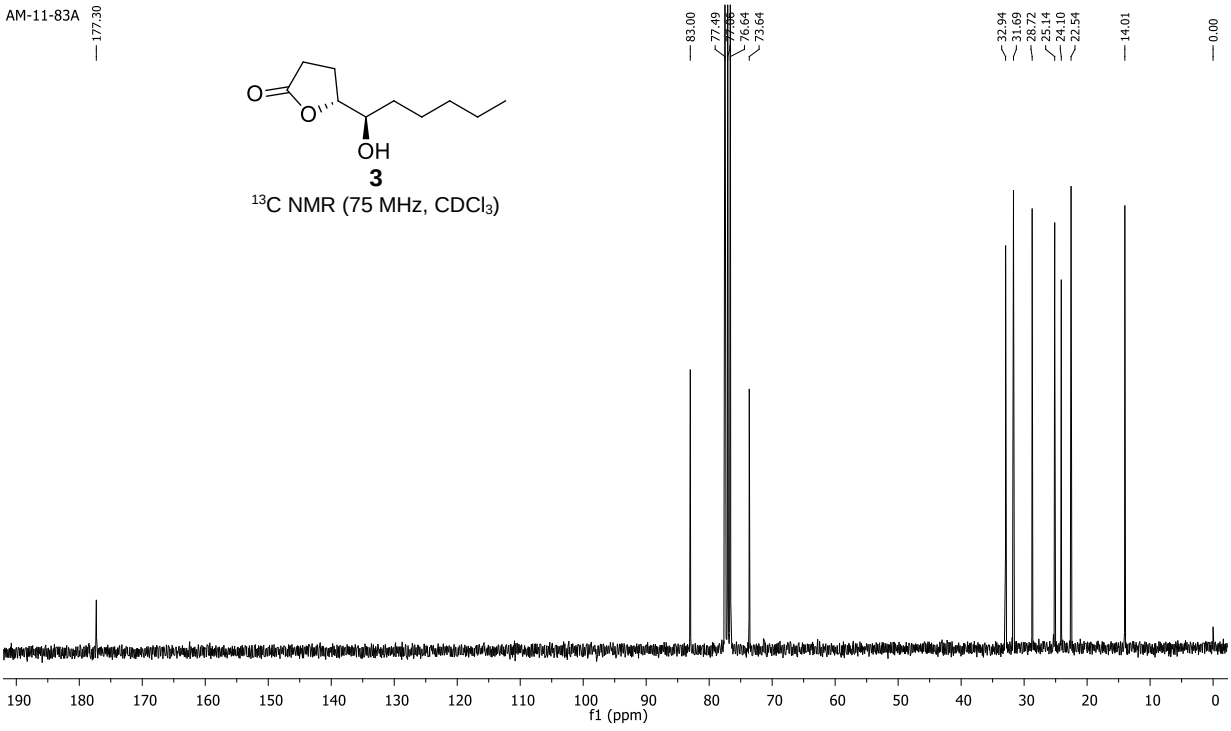

AM-11-81
207.41
176.05
81.79
77.51
77.09
76.67
38.80
31.23
27.38
24.61
22.55
22.40
13.88
-0.00
O
O
O
55
13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)





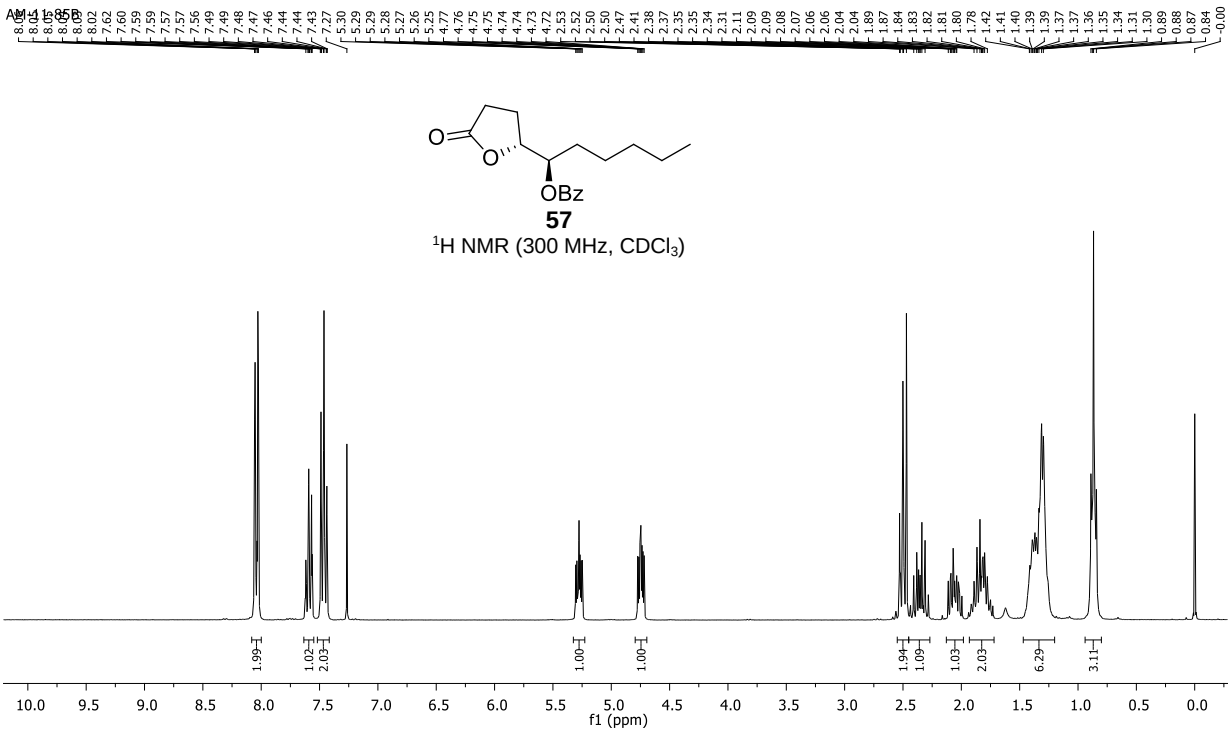
3

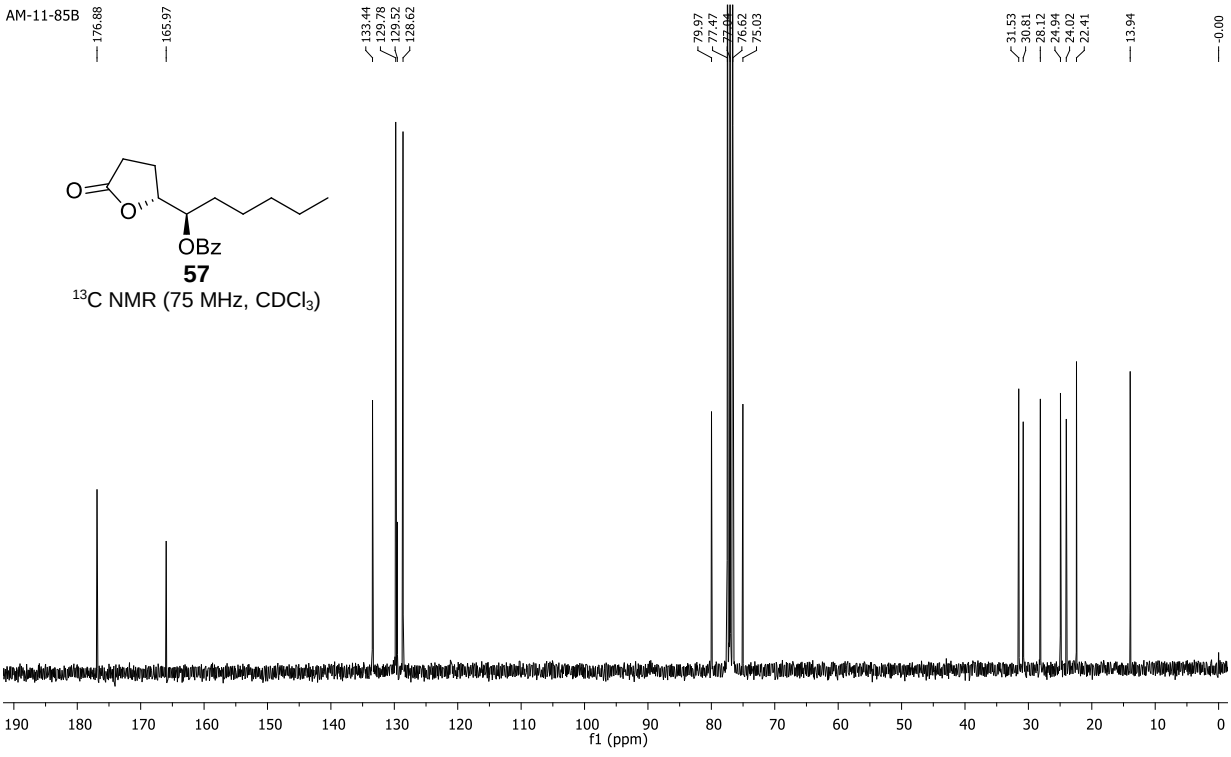
^{1}H NMR (300 MHz, $CDCl_3$)



3

^{13}C NMR (75 MHz, $CDCl_3$)


AM-11-85B
OBz
57
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)


AM-11-85B
OBz
57
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

5.10 Selected HPLC traces

Memorial University

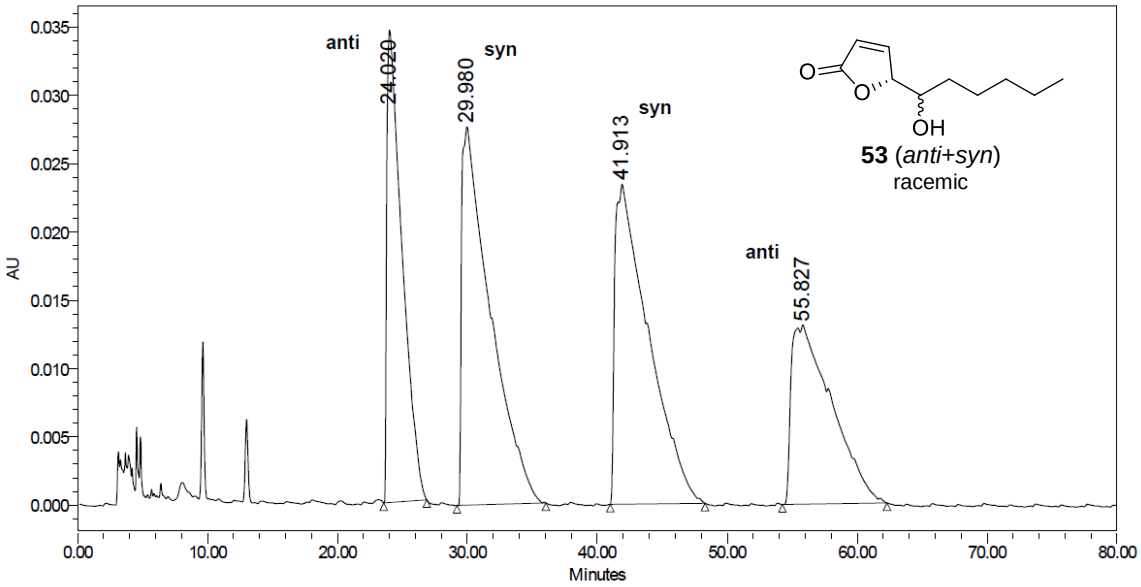
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-11-59	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/04/2017 12:31:51 PM NDT
Vial:	1	Acq. Method:	AS_H95Hex5IPA
Injection #:	1	Date Processed:	11/04/2017 2:05:25 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	80.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	24.020	2826860	20.05	34582	34.99
2	29.980	4227396	29.99	27701	28.03
3	41.913	4201517	29.81	23434	23.71
4	55.827	2839986	20.15	13126	13.28

Memorial University

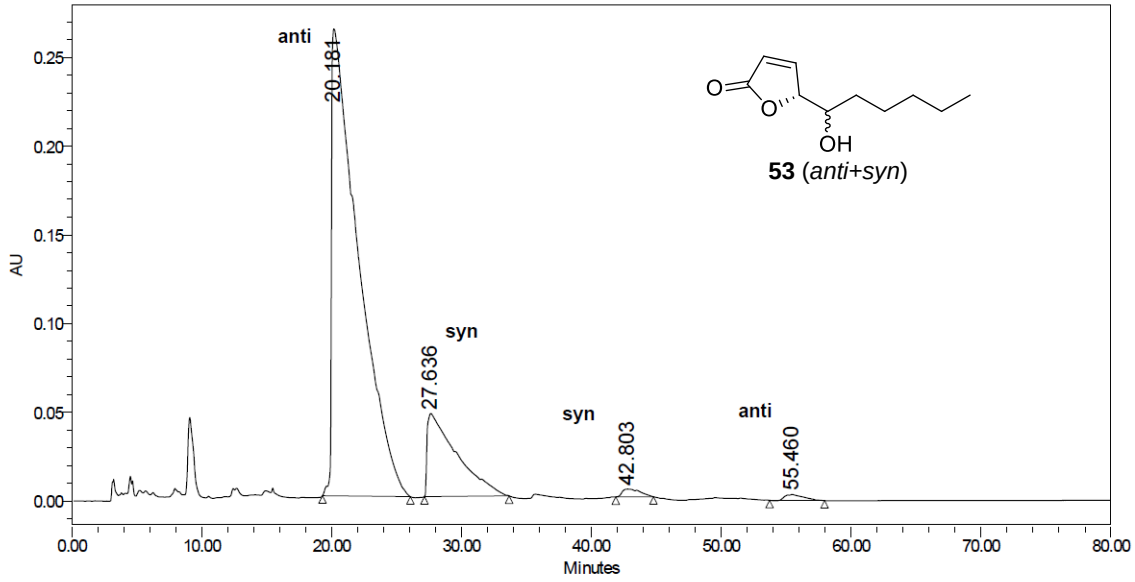
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-11-73	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	02/05/2017 12:28:14 PM NDT
Vial:	1	Acq. Method:	AS_H95Hex5IPA
Injection #:	1	Date Processed:	02/05/2017 1:50:15 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	80.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



53 (*anti*+*syn*)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	20.181	37672247	82.22	263254	82.84
2	27.636	7384098	16.12	46783	14.72
3	42.803	419203	0.91	4386	1.38
4	55.460	342860	0.75	3375	1.06

Report Method: Individual Control Report

Page: 1 of 1

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12:19:04 PM Canada/Newfoundland

Memorial University

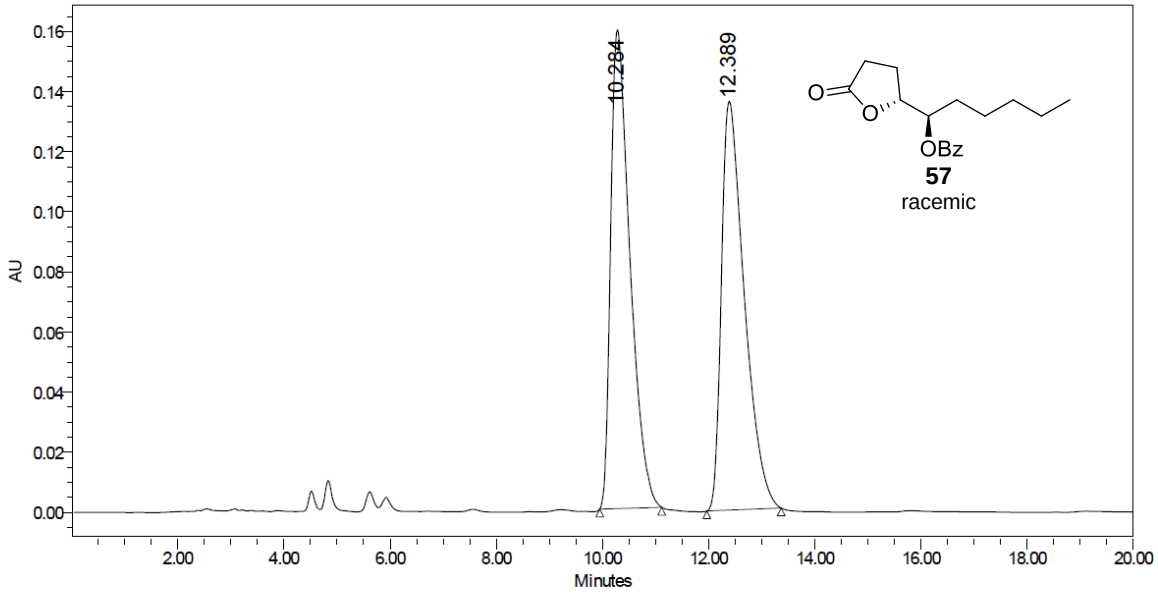
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-11-85B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	26/04/2017 2:31:37 PM NDT
Vial:	1	Acq. Method:	OD_H 97%Hex3%IPA
Injection #:	1	Date Processed:	26/04/2017 3:06:20 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.284	4021805	49.75	159355	53.93
2	12.389	4062279	50.25	136138	46.07

Report Method: Individual Control Report

Page: 1 of 1

Printed: 13/05/2017

11:27:25 AM Canada/Newfoundlanc

Memorial University

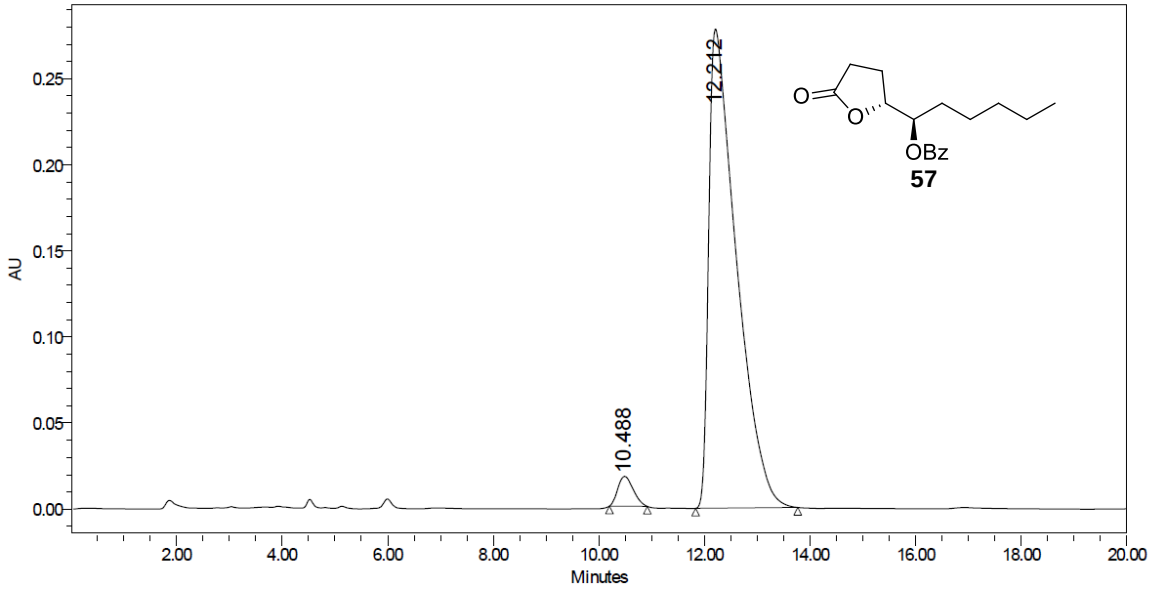
Project Name AMARENDER

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	AM-11-95B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	13/05/2017 11:11:39 AM NDT
Vial:	1	Acq. Method:	OD_H 97%Hex3%IPA
Injection #:	1	Date Processed:	13/05/2017 11:32:23 AM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.488	350776	3.35	17346	5.87
2	12.212	10107812	96.65	278322	94.13

Report Method: Individual Control Report

Page: 1 of 1

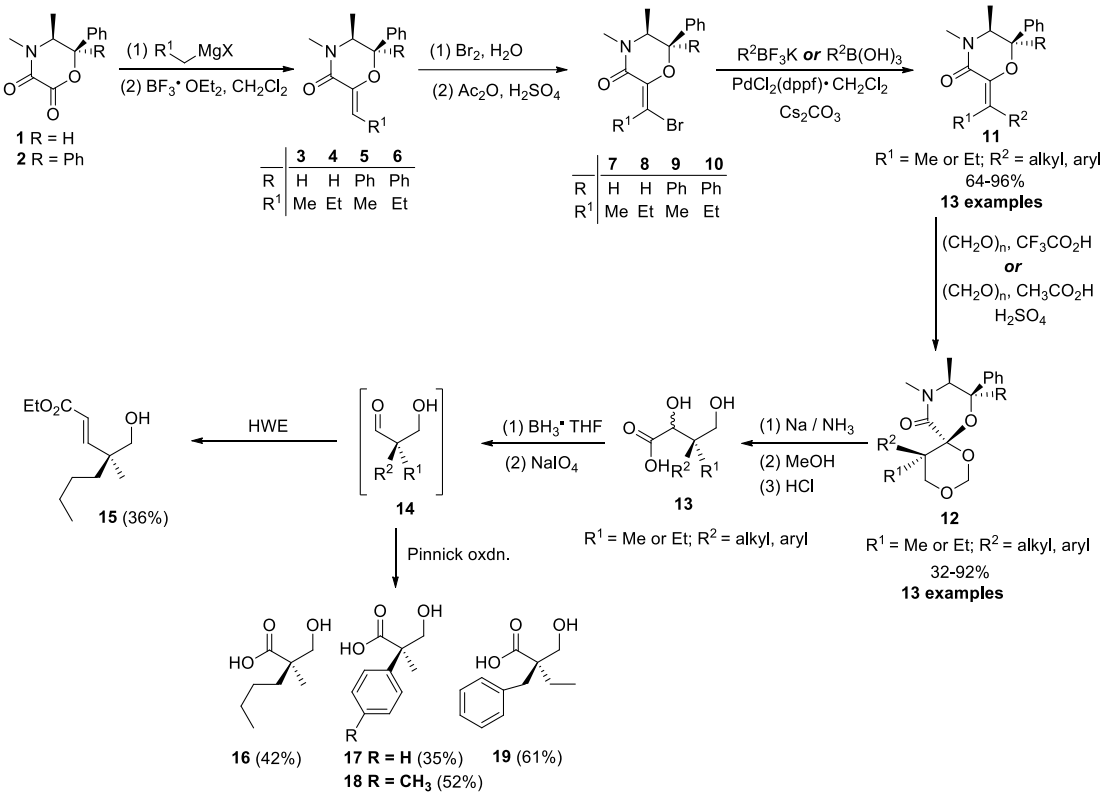
Printed: 13/05/2017 11:33:22 AM Canada/Newfoundlanc

Chapter 6

Conclusions

6.1 Summary of the thesis

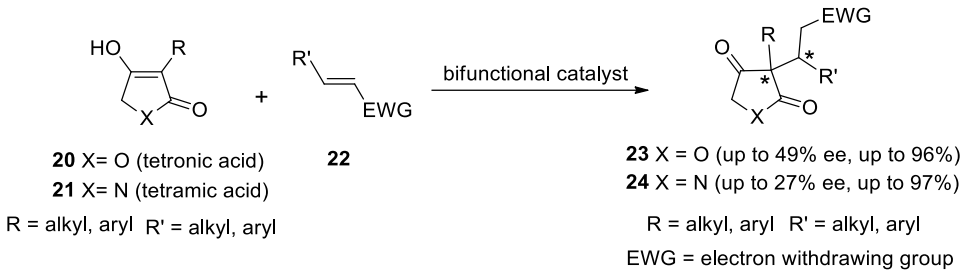
An enantioselective synthesis of functionalized quaternary stereocenters was developed from chiral amino alcohol-derived (bromoalkylidene)morpholinones (**7-10**, Scheme 6.1). The stereoselective cross-coupling of the morpholinones (**7-10**) with arylboronic acids or alkyl trifluoroborates provided a variety of disubstituted alkylidenemorpholinones (**11**) in 64-96% yields as single diastereomers. A highly stereoselective Prins reaction of the cross-coupling products (**11**) generated spiro dioxanyl-morpholinones (**12**, in 32-92% yields) bearing the target quaternary stereocenter. Prins adducts (**12**) are readily converted to a variety of enantiomerically enriched aldehydes, acyclic carboxylic acids (**16-19**), or their derivatives (**15**), all possessing a quaternary stereocenter. The compound**s** (**15-19**) can be used as starting materials for the synthesis of small organic molecules with quaternary stereocenters or they can be incorporated into more complex structures. The methyl ester of the hydroxy acid **18** (Scheme 6.1) prepared in this study is a key component for the total synthesis of (+)-α-cuparenone. The results of this work are described in Chapter 1.



Scheme 6.1 Synthesis of functionalized quaternary stereocenters

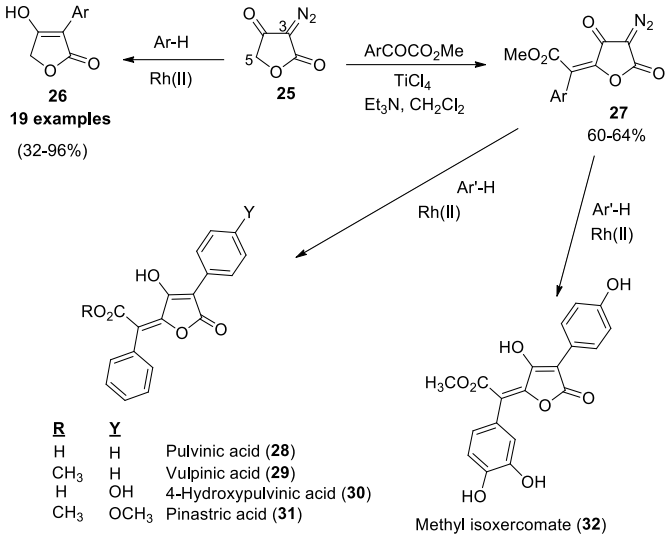
In a separate approach, the enantioselective synthesis of functionalized quaternary centers-containing furan-2,4(3*H*,5*H*)-diones (**23)** and pyrrolidine-2,4-diones (**24)** has been investigated and details of the studies undertaken are described in Chapter 2. The approach relies on the conjugate addition of a variety of 3-alkyl/aryltetronic acids (**20)** and 3-alkyl/aryltetramic acids (**21**) to a selection of *α,β*-unsaturated systems (**22**, Michael acceptors) using bifunctional, chiral catalysts such as aminothioureas and aminosquaramides. These reactions were feasible with the vast majority of chiral catalysts that were examined, and they provided the expected Michael adducts in good yields (up to 96% for tetronic acids and up to 97% for tetramic acids, Scheme 6.2), but with low to moderate enantiomeric excess (up to 49% ee for tetronic acids and up to 27% ee for tetramic

acids). Further optimization of these reactions is required, and these studies are continuing in the Pansare group. The enantiomerically-enriched Michael adducts **23** are key intermediates for the asymmetric syntheses of natural products[1] such as fraxinellonone, saudin, trisporic acids A-B and (+)-cassiol.



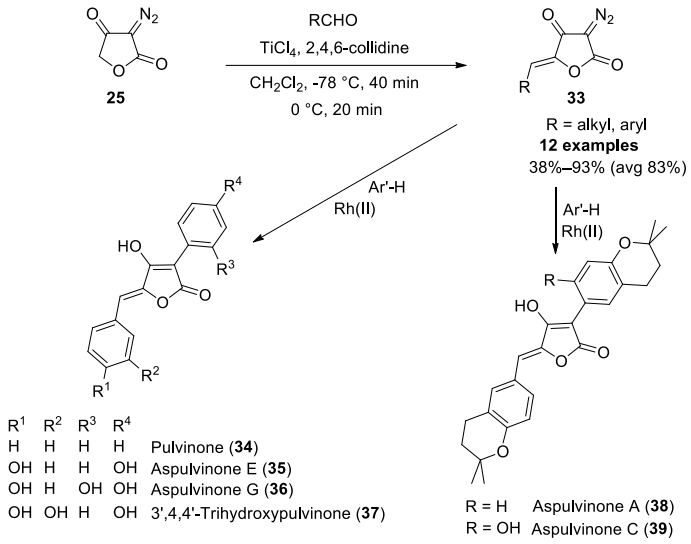
Scheme 6.2

A variety of 3-aryltetronic acids (**26**) were synthesized by employing an undirected, intermolecular C−H functionalization reaction of arenes with 3-diazofuran-2,4-dione (**25**) as the key step. This method was applied in the synthesis of a series of naturally occurring 3-aryl-5-arylidene tetronic acids such as pulvinic acids and vulpinic acids (**28**-**32**). Salient features of the methodology include a highly stereoselective aldol condensation of **25** with α-keto esters for installation of the C5 arylidene functionality and a single step introduction of the C3 aryl substituent. Chapter 3 of this thesis describes the details of this methodology and its applications.



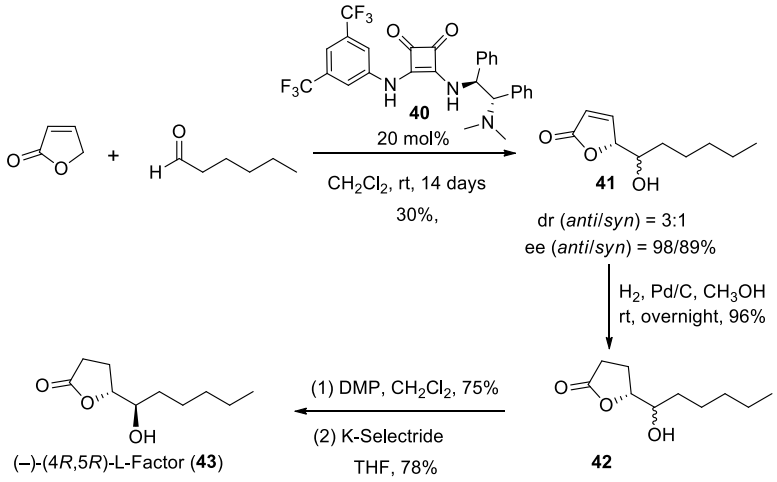
Scheme 6.3 Synthesis of pulvinic acids and vulpinic acids

An application of the above methodology in the synthesis of a variety of naturally occurring pulvinones **34-39** has also been investigated. This synthetic approach follows highly stereoselective aldol condensation of **25** with a variety of aliphatic or aromatic aldehydes under optimized conditions ($TiCl_4$, 2,4,6-collidine) to provide (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones **33** in excellent yields (12 examples, 83% average yield, Scheme 6.4) as single diastereomers. Diones **33** are the immediate precursors of the required pulvinone natural products. The aryl substituents at C3, required in the targeted pulvinones, were installed by employing undirected, intermolecular C−H insertion reactions. Six naturally occurring pulvinones, **34-39** (Scheme 6.4), were synthesized using this strategy. Details of this study are described in Chapter 4.



Scheme 6.4 Synthesis of naturally-occurring pulvinones

A concise, four step enantioselective synthesis of (4*R*,5*R*)-L-factor (**43**) was achieved by employing the organocatalytic direct vinylogous aldol reaction of γ-crotonolactone with hexanal using aminosquaramide catalyst **40** (Scheme 6.5). This synthetic strategy follows the vinylogous direct aldol reaction of γ-crotonolactone with hexanal to provide **41** with excellent ee. Compound **41** was converted into (4*R*,5*R*)-L-factor (**43**) in three steps, namely, hydrogenation, DMP oxidation and a highly diastereoselctive K-selectride reduction of the ketone obtained by the DMP oxidation. Details of the synthesis are described in Chapter 5 of this thesis.

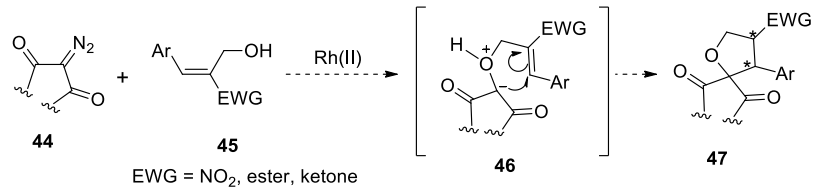


Scheme 6.4 Synthesis of (−)-(4*R*, 5*R*)-L-factor

In summary, the work described in this thesis has developed an enantioselective synthesis of functionalized quaternary stereocenters, a one-step synthesis of a variety of 3-aryltetronic acids and natural (pulvinic acids and pulvinones) as well as non-naturally-occurring tetronates from 3-diazofuran-2,4-dione, and also a short synthesis of L-factor.

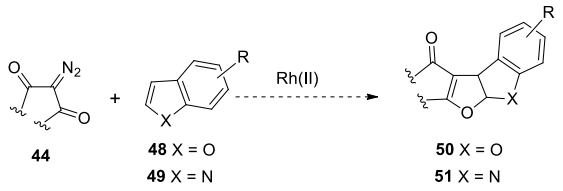
6.2 Future Work

Functionalised furans are important building blocks in organic synthesis. Such furans **47**, can be easily synthesized from diazo 1,3-dicarbonyl (**44)** and *β,γ*-unsaturated alcohol (**45**, Scheme 6.6). This reaction is expected to proceed through an initial OH insertion [2] reaction followed by an intramolecular conjugate addition to provide functionalized furans.



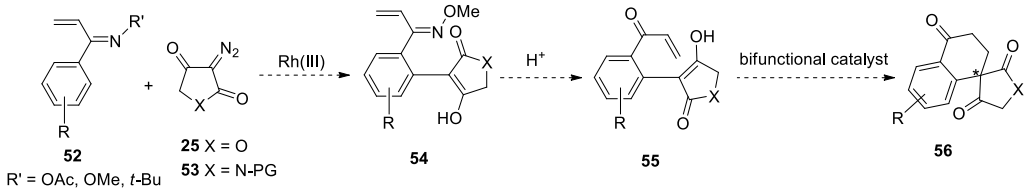
Scheme 6.6

Furoindolines (**50**) and pyrroloindolines (**51**) are found as key structural units in a large number of indole alkaloids.[3] These structural motifs can be potentially synthesized by metal-catalyzed 1,3 dipolar cycloadditions[4] of diazo 1,3-dicarbonyl compounds (**44**) with various benzofurans (**48**) and indoles (**49**), respectively (Scheme 6.7).



Scheme 6.7

The importance of the enantiomerically enriched, functionalised quaternary stereocenters is mentioned in Chapters 1 and 2 of this thesis. One possible approach to functionalized quaternary stereocenters is shown in Scheme 6.8. The methodology relies on directed C-H insertion[5] reactions of an oxime derivative such as **52** with diazo compounds **25** or **53** to provide **54**. Hydrolysis[6] of the oxime should provide **55**. Intramolecular Michael addition reactions of these tetronic or tetramic acids **55** in the presence of chiral bifunctional catalysts can provide enantiomerically enriched quaternary stereocenter-containing furan-2,4-diones or pyrrolidine-2,4-diones **56** (Scheme 6.8).



Scheme 6.8

6.3 References

1. (a) Ramachary, D. B.; Kishor, M. *Org. Biomol. Chem.*, **2010**, *8*, 2859. (b) Bacigaluppo, J. A.; Colombo, M. I.; Cravero, R. M.; González-Sierra, M.; Preite, M. D.; Zinczuk, J.; Rúveda, E. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1877. (c) Bacigaluppo, J. A.; Colombo, M. I.; M.; Preite, M. D.; Zinczuk, J.; Rúveda, E. A. *Tetrahedron: Asymmetry* **1996**, *7*, 1041. (d) Winkler, J.D.; Doherty, E. M. *J. Am. Chem. Soc.*, **1999**, *121*, 7425. (e) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.*, **2005**, ***7***, 2413. (f) Colombo, M. I.; Zinczuk, J.; Bohn, M. L.; Ruveda, E. A. *Tetrahedron: Asymmetry* **2003**, *14*, 717. (g) Okamura, H.; Yamauchi, K.; Miyawaki, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett*. **1997**, *38*, 263. (h) White, J.D.; Takabe, K.; Prisbylla, M.P. *J. Org. Chem.* **1985**, *50*. 5233.
2. Jiang, L.; Xu, R.; Kang, Z.; Feng, Y.; Sun, F.; Hu, W. *J. Org. Chem.*, **2014**, *79*, 8440.
3. Liu, C.; Yin, Q.; Dai, Li-X.; You, S.-Li. *Chem. Commun.*, **2015**, *51*, 5971.
4. (a) Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112; (b) Pirrung, M. C.; Zhang, J.; McPhail, A. T. J. Org. Chem. **1991**, *56*, 6269.
5. (a) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (b) Ng, K-H.; Zhou, Z.; Yu, W-Y. *Org. Lett.* **2012**, *14*, 272.
6. Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.*, **1997**, *62*, 5647.